AMINO-FUNCTIONAL CHALCONES

FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues thereto as well as to use of a class of chalcone derivatives as pharmaceutically active agents, in particular against bacterial and parasitic infections.

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism such as *Helicobacter pylori* and *Plasmodium falciparum*. The prediction is based on the ability of the chemical compound to act as an inhibitior of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells.

BACKGROUND OF THE INVENTION

Chalcones, e.g., for use against parasitic infections are known from earlier patent applications assigned to the applicant, e.g. WO 93/17671 and WO 99/00114. Moderate antibacterial activity has been reported for a limited number of chalcones in earlier publications e.g. Haraguchi, H. et al *Phytochemistry* 1998, *48*, 125-129 and Hatano, T. et al *Chem. Pharm. Bull (Tokyo)* 2000,*48*, 1286-92.

The bioavailability of several of the known chalcones is low due to the low solubility of the compounds. The compounds do not typically dissolve in the intestine and are therefore not available for absorption.

The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem. Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β-lactam-antibiotics and Enterococci resistant to vancomycin (VRE). Such resistant bacteria pose a significant therapeutic challenge and bacterial strains resistant to all currently available antimicrobials are emerging. Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients. An example of this is *Stenotrophomonas maltophilia* which possesses a β-lactamase rendering the bacteria intrinsically resistant to carbapenems. As cross-resistance within a given class of antibiotics often occurs the development of new classes of antibiotics is a neccisity to counter the emerging threat of bacterial resistance.

The resistance of *Plasmodium falciparum* to chloroquine and other antimalarial drugs have created an urgent need for new drugs that are safe and effffective for the prophylaxis and treatment of malaria.

Furthermore, the increasing appearance of resistance to first line antileishmanial drugs, e.g. Pentostam or Glucantime, emphasizes the need for new drugs for the treatment of *Leishmania* infections.

Thus, there is a need for chalcone derivatives with improved therapeutic or prophylactic activity against parasites and bacteria.

Chalcones carrying certain amino substituents are known from Dimmock et al (J. Med. Chem. 1998, 41, 1014-26) and Cain et al (US5523302).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of amino-functional chalcones where the aromatic rings are phenyl rings. R^1, R^2, and Z are as defined herein.

Figure 2 illustrates the synthesis of amino-dihydrochalcones. R^1, R^2, and Z are as defined herein.

Figure 3 illustrates a time-kill curve of A031 against S.aureus ATCC29213. Bacterial growth is inhibited at concentrations at or above the MIC (MIC=9.4 μM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

Figure 4 illustrates a time-kill curve of A019 against S.aureus ATCC29213. Bacterial growth is inhibited at concentrations of test compound at or above the MIC (MIC=9.4 μM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The rate of reduction of CFU/ml is not significantly affected by increasing concentrations of test compound. Thus, the bactericidal action of the compound is primarily dependent on incubation time.

Figure 5 illustrates a dose-response curve of Licochalcone A (LicA) and one of the novel amino-chalcones (A139) at *Plasmodium falciparum*. As shown at the figure, A139 is 18 times more potent than LicA.

Figure 6 illustrates a dose-respons curve of LicA and one of the novel amino-chalcones A037 at *Leishmania Major*. As shown at the figure, A037 is 46 times more potent than LicA.

Figure 7 illustrates an effect curve of A027 in *Plasmodium berghei* K173 infected NMRI female mice following multiple intra venous administrations. As shown at the figure, treatment with A027 causes a significant decrease in the parasitaemia.

Figure 8 illustrates an effect curve of A027 in *Plasmodium berghei* K173 infected NMRI female mice following multiple oral administrations. As shown at the figure, treatment with A027 causes a significant decrease in the parasitaemia.

DESCRIPTION OF THE INVENTION

The present inventors have found that the amino-functional chalcones defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents.

It is believed that the amino group or groups of the amino-functional chalcone will be charged according to pH of the medium and the pKa of the compound. The solubility of the charged compounds is significantly higher than the solubility of the neutral compounds. As the amino-functional chalcones will be partially charged and thus soluble in aqueous solutions at physiological pH values in the intestine or stomach, they will dissolve in the gastric juices and then be available for absorption. The bioavailability of the amino-functional chalcones will therefore be improved compared to the known neutral chalcones, thus making the compounds generally useful as drug candidates. Also, the present amino-functional chalcones possess different pKa values which allows the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value.

Furthermore, the application of the known chalcones as drug candidates have been limited due to extensive metabolism of the compounds, which results in short half-lives *in vivo*. The present inventors have now found that introduction of an amino group in the chalcone molecule affects the metabolic properties so as to achieve improved metabolic stability.

The introduction of an alifatic amino-group and hence a positive charge (at the pH value of the target site) affects the mode of interaction with the biological target. It is anticipated that the compounds interact with the target in a different way than neutral chalcones, due to the possibility of strong electrostatic interactions (attraction as well as repulsion). This is indeed reflected in the activity of the compounds, being more potent than the previously described neutral chalcones.

Of particular interest, the present inventors have found that the amino-functional chalcones defined herein are far more potent against malaria and leishmania parasites than the earlier described neutral chalcone compounds, and that they exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains.

Thus, in a first aspect, the present invention provides chalcone derivatives and analogues of the general formula:

$$(Y^1)_m\text{-}Ar^1(X^1)\text{-}C(=O)VAr^2(X^2)\text{-}(Y^2)_p$$

wherein Ar^1 and Ar^2 independently may be selected from aryl or heteroaryl;

V designates $-CH_2-CH_2-$, -CH=CH- or -C≡C-, preferably -CH=CH-;

m is 0, 1, or 2,

p is 0, 1, or 2,

wherein the sum of m and p is at least 1;

each Y^1 is independently selected from an amino-functional substituent of the formula

$$-Z-N(R^1)R^2,$$

each Y^2 is independently selected from an amino-functional substituent of the formula

$$-Z-N(R^1)R^2,$$

wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, and each R^H is independently selected from hydrogen or C_{1-6}-alkyl, or two R^H on the same carbon atom may designate =O;

R^1 and R^2 independently may be selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, or mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl,

or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring;

X^1 and X^2 independently may designate 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted

heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, or halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine;

and salts thereof.

The substituents R^1 and R^2 carried by the nitrogen atom of the amino substituent are believed to slightly alter the pKa value of the chalcone derivative. Thus, the particular selection of the groups R^1 and R^2 may be used to "fine-tune" the pKa value in view of the particular condition or disease and the intended route of administration.

In one embodiment, R^1 and R^2 may be independently selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl. In particular R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6}-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, or mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl.

In another embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached (-N(R^1)R^2) form an optionally substituted nitrogen-containing heterocyclic ring.

In still a further embodiment, X^1 and X^2 independently may designate 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently may be selected from optionally substituted C_{1-12}-alkyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino,

optionally substituted (heteroarylalkyl)alkylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, guanidino, carbamido, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, optionally substituted C_{1-6}-alkylthio, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen, in particular X^1 and X^2 independently designates 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, C_{1-6}-alkyl-carbonylamino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen.

In a suitable embodiment, X^1 and X^2 independently designates 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino , cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl-oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with

hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, carboxy, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

In a particular embodiment, X^1 and X^2 independently may designate 0-3, e.g. 0-2, substituents, where such optional substituents may independently be selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, amino, mono- and di(C_{1-6}-alkyl)amino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, carbamoyl, C_{1-6}-alkyl-carbonylamino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with at least one substituent selected from the group consisting of hydroxy, C_{1-6}-alkoxy, or halogen.

The group V is relevant with respect to the spatial orientation of the rings Ar^1 and Ar^2. Thus, the group V may be $-CH_2-CH_2-$, -CH=CH- or -C≡CIn a currently interesting embodiment thereof, V designates -CH=CH-.

In the context of the present invention, the expression "chalcone derivative" is to be assigned to the compounds of the above formula in that the overall structure namely Ar^1-C(=O)-C-C-Ar^2 resembles that of the chalcone structure. This being said, Ar^1 and Ar^2 are selected from aromatic rings and heteroaromatic rings. It is currently believed that particularly interesting compounds are those where at least one of Ar^1 and Ar^2, preferably both, are aryl, in particular phenyl. This being said, the inventors envisage that the functionality of the compounds may be substantially preserved (or even improved) when one or both of Ar^1 and Ar^2 are heteroaromatic rings.

In one embodiment, at least one of Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, quinolyl, isoquinolyl, and indolyl.

In another embodiment, both of Ar^1 and Ar^2 are phenyl rings and Y^1 represent at least one amino-functional substituent, i. e. m is 1 or 2, and p is 0.

In a further embodiment, X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen.

In a yet further embodiment, X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C_{1-6}-alkyl)amino, optionally substituted heterocyclyl and halogen.

The Z group represents the biradical between the ring and the amino functionality. This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 1-4, such as 1-3, where each R^H is independently selected from hydrogen and C_{1-6}-alkyl, or two R^H on the same carbon atom may designate =O. A particular example of Z is $-(CH_2)_n-$ wherein n is 1-4, such as 1-3.

Thus, in a particular embodiment, one of Y^1 and Y^2 represent a substituent of the formula

$$-CH_2-N(R^1)R^2$$

wherein R^1 and R^2 is selected from hydrogen and C_{1-6}-alkyl. Furthermore, V is preferably -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings. In a particular embodiment, Y^1 represents the substituent fo the formula $-CH_2-N(R^1)R^2$.

In one preferred embodiment, m is 1 and p is 0. In another preferred embodiment m is 0 and p is 1. In a further interesting embodiment, m and p are both 1.

In a further typical embodiment, where Ar^1 and Ar^2 are both phenyl, V is -CH=CH-, Z is CH_2, R^1 and R^2 are methyl or together form a morpholino group, and one of m and p is 2 while the other of m and p is 0,

X^1 and X^2 independently may designate 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, where such optional substituents may independently be selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, 2-, 3-, 5-, or 6-hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, heteroarylsulphonylamino, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and

di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino , cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyl-oxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, or halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, carboxy, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine;

provided that

when Ar^1 and Ar^2 are both phenyl, V is -CH=CH-, m is 1, p is 0, Y1 is 2-CH2NMe2, and X2 is absent, then X1 is not solely 4-methoxy;

when Ar^1 and Ar^2 are both phenyl, V is -CH=CH-, m is 1, p is 0, Y1 is 3- or 4-CH2NR1R2, wherein R1 and R2 are selected from hydrogen, methyl, and ethyl, and X1 is solely 4-hydroxy or 4-alkoxy, or absent, then X2 is not solely nitro, dichloro, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 2-carboxyethyl, or absent;

when Ar^1 and Ar^2 are both phenyl, V is -CH=CH-, m is 0, p is 1, Y^2 is solely 2- or 3-$CH_2NR^1R^2$, wherein R^1 and R^2 are selected from hydrogen, methyl, and ethyl, and X^2 is solely 4-OH, or absent, then X^1 is not solely ethoxycarbonylmethoxy, dichloro, or absent.

Generally preferred compounds may, e.g., be selected from the group comprising:

1-(4-Methoxy-phenyl)-3-(4-morpholin-4-ylmethyl-phenyl)-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-(4-propylaminomethyl-phenyl)-propenone,
3-(4-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
3-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-(4-piperidin-1-ylmethyl-phenyl)-propenone,
3-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
3-(4-Dibutylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
3-{4-[(4-Diethylamino-1-methyl-butylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
3-{3-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-(3-propylaminomethyl-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(4-Methoxy-phenyl)-3-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone,
1-(2-Bromo-phenyl)-3-(2-dimethylaminomethyl-phenyl)-propenone,
3-{3-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,

3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone ,
3-(2,4-Dichloro-phenyl)-1-{3-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone ,
3-(2,5-Dimethoxy-phenyl)-1-{4-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone ,
3-(4-Dibutylamino-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,5-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dibutylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-pyridin-2-yl-propenone,
3-(4-Dibutylamino-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone,
3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-(2,4-dichloro-phenyl)-propenone,
Acetic acid 1-{2-[3-(2,4-dichloro-phenyl)-acryloyl]-benzyl}-piperidin-4-yl ester,
3-(2,4-Dichloro-phenyl)-1-(2-morpholin-4-ylmethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-o-tolyl-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-methoxy-phenyl)-propenone,
3-(4-Chloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Difluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(3-Butylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-diethylaminomethyl-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-hydroxy-2-methoxy-5-propyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-fluoro-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-[2-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propenone,
1-(3-Diethylaminomethyl-phenyl)-3-(2,5-dimethoxy-phenyl)-propenone,
3-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(4-Imidazol-1-yl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-2-yl-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-3-yl-propenone,

1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-4-yl-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1-methyl-1H-pyrrol-2-yl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1H-pyrrol-2-yl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-thiophen-2-yl-propenone,
1,3-Bis-(2-diethylaminomethyl-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-diethylaminomethyl-phenyl)-propenone,
3-(4-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(2-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-[3-(Butyl-ethyl-amino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(3-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2-Diethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1,3-Bis-(2-dimethylaminomethyl-phenyl)-propenone,
3-(4-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
3-(1H-Indol-5-yl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2,4-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-imidazol-1-yl-phenyl)-propenone,
1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-{3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-oxo-propenyl}-benzoic acid,
1-(2-Dimethylaminomethyl-phenyl)-3-(2,4-dimethyl-phenyl)-propenone,
3-(2,4-Dimethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(1-methyl-1H-pyrrol-2-yl)-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-ethoxy-phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(3-Dimethylaminomethyl-4-methoxy-phenyl)-1-(4-methoxy-phenyl)-propenone,
1-(2-Methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-3-ylamino)-phenyl]-propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-(3-morpholin-4-ylmethyl-phenyl)-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-(4-pyridin-2-yl-phenyl)-propenone,

1-(4-Methoxy-phenyl)-3-(3-{[methyl-(2-methylamino-ethyl)-amino]-methyl}-phenyl)-propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone,
3-(2-Dimethylaminomethyl-phenyl)-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-(3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-(3-methylaminomethyl-phenyl)-propenone,
1-(3-Dimethylaminomethyl-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone,
3-{3-[(2-Methoxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[2-methoxy-5-(pyridin-3-ylamino)-phenyl]-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propanone,
3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
1-(4-Methoxy-phenyl)-3-(3-piperazin-1-ylmethyl-phenyl)-propenone,
3-(3-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone,
3-(3-{[(2-3-{3-[(2-Hydroxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone,
3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2-fluoro-4-methoxy-phenyl)-propenone,
3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone,
3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone,
3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone,
3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone,
1-[4-(2-Dimethylamino-ethyl)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone,
3-(4,2'-Dimethoxy-biphenyl-3-yl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone,
3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2,3,4-trimethoxy-phenyl)-propenone,
3-(2,5-Dimethoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
3-(3',5'-Dichloro-4,6-dimethoxy-biphenyl-3-yl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone,
3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-{3-[(pyridin-3-ylmethyl)-amino]-phenyl}-propenone,

1-(2-Dimethylaminomethyl-phenyl)-3-{3-[(pyridin-3-ylmethyl)-amino]-phenyl}-propenone,
1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]-propenone,
1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]- propenone,
3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone,
3-(5-tert-Butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone,
3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone,
or
3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-phenyl)-propenone.

While the above-mentioned group of compounds is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms, a generally preferred embodiment of the above-mentioned compounds has the *E*-configuration at the enone functionality.

In a further aspect, the invention further provides combinatorial libraries, mixtures and kits for screening compounds as defined above.

In one embodiment, a combinatorial library comprising at least two compounds of the general formula is provided. Such library may be in the form of an equimolar mixture, or in a mixture of any stoichiometry. Typical embodiments comprise at least two, such as at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above.

In another embodiment, combinatorial compound collections in the form of kits for screening for biologically or pharmacologically active compounds are provided. Such kits comprise at least two topologically distinct singular compounds of the general formula defined above. Typical kits comprise at least 10, such as at least 100, such as at least 1000, such as at least 10000, such as at least 100000 compounds as defined above. Kits are preferably provided in the form of solutions of the compounds in appropriate solvents.

Further provided are methods for screening for pharmacologically active compounds, especially bacteriostatic, bacteriocidal and antiparasitic agents, consisting of the steps of preparing a kit or library comprising at least two compounds of the general formula defined above, contacting said kit or library with a target molecule, such as a protein or nucleic acid, a target tissue, or a target organism, such as a bacterium or parasite, and detecting a biological or pharmacological response caused by at least one compound. Optionally, the steps may be repeated as appropriate to achieve deconvolution.

Definitions

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compund, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time.

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time.

In the present contest, the term "antiparasitic" is intended to describe the ability of a test compound to upon incubation in vitro with a culture of parasites, e.g. *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures.

In the present context, the term "C_{1-12}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc. Analogously, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C_{1-4}-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

Whenever the term "C_{1-12}-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C_{1-6}-alkyl".

Similarly, the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", and "C_{6-12}-alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C_{2-12}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

Whenever the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", "C_{6-12}-alkatrienyl", and "C_{2-12}-alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms.

In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

Especially preferred examples are hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, and guanidine.

The terms "optionally substituted C_{1-12}-alkoxy" and "optionally substituted C_{1-6}-alkoxy" are intended to mean that the alkoxy groups may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality),

C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylcarbonyl, heteroaryl, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl.

Especially preferred examples of "optionally substituted C_{1-12}-alkoxy" and "optionally substituted C_{1-6}-alkoxy" groups are unsubstituted such groups as well as those carrying one or two substituents selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, carboxy, halogen, or C_{1-6}-alkylthio.

"Halogen" includes fluoro, chloro, bromo, and iodo.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or –NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thienyl, quinolyl, tetrazolyl, and isoquinolyl.

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or –NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples

are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, when appled to groups of aromatic character, i.e. in connection with the terms "aryl", "heteroaryl", "heterocyclyl", "heteroarylamino", "(heteroarylalkyl)amino", "(heteroarylalkyl)alkylamino", etc, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

Preferably, the substituents are selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine. Especially preferred examples are C_{1-6}-alkyl, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present. Such a

nitrogen is, with reference to the formula, carrying the substituents R_1 and R_2. The "nitrogen-containing heterocyclic ring" may further comprise additional heteroatoms, e.g. nitrogen (=N- or -N-), sulphur, and/or oxygen atoms. Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxozole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole. The most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole.

Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, and thiazetane. The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the same substituents as defined above for "optionally substituted aryl".

As is evident from the formulae defined herein and the definitions associated therewith, certain compounds of the present invention are chiral. Moreover, the presence of certain cyclic fragments or multiple stereogenic atoms provides for the existence of diastereomeric forms of some of the compounds. The invention is intended to include all stereoisomers, including optical isomers, and mixtures thereof, as well as pure, partially enriched, or, where relevant, racemic forms.

Embodiments where V is -CH=CH- may comprise *E*- and *Z*-stereoisomers, or mixtures of such isomers, which may exist in a dynamic equilibrium is solution. The *E*-isomers are generally preferred.

It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples

of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^{+}N(R')_4$), where the R's independently designate optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R.Gennaro (Ed.), Lippincott, Williams & Wilkins; ISBN: 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology. However, generally preferred salt forming agents for application in the present invention are organic dicarboxylic acids such as oxalic, fumaric, and maleic acid, and the like.

Thus, chalcones with amino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations. The use of appropriate selected salt form can be used to control the dissolution rate in vivo. Furthermore, the different salt forms have different bulk-properties which is of importance for the manufacturing process.

Preparation of compounds

The amino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods. Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following. Further examples of methods for the preparation of the compound used according to the present invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein.

Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a ketone (an acetophenone in the case where Ar^1 is phenyl)

$$(Y^1)_m\text{-}Ar^1(X^1)\text{-}C(=O)\text{-}CH_3$$

with an aldehyde (a benzaldehyde in the case where Ar^2 is phenyl)

$$HCO\text{-}Ar^2(X^2)\text{-}(Y^2)_p$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, Y^2, m, and p refer to the definitions given elsewhere herein.

This reaction, which is a condensation reaction, is suitably carried out under acid or base catalysed conditions. A review of such processes may be found in Nielsen, A.T., Houlihahn, W.J., *Org. React.* **16**, 1968, p 1-444. In particular the method described by Wattanasin, S. and Murphy, S., *Synthesis* (1980) 647 has been found quite successful. The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e.g. methanol,

ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e.g. dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene or benzene), or mixtures of such solvents. When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum, ammonium, or quaternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides or methylphenyl amides). Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used.

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3, $POCl_3$, PCl_5, or $FeCl_3$), or acid ion exchange resins.

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy groups. This drawback can be overcome by masking the phenolic group as described by T. Hidetsugu et al. in EP 0 370 461. Deprotection is easily performed by mineral acids such as hydrochloric acid.

The reaction is typically carried out at temperatures in the range of 0-100°C, e.g. at room temperature. Reaction times are typically from 30 min to 24 hours.

The alkyl- or dialkyl aminomethyl-acetophenones and -benzaldehydes were prepared by reductive amination using substituted benzaldehyde, amine and sodium triacetoxyborohydride. The alkyl- or dialkyl aminoalkyl-acetophenones and -benzaldehydes were prepared from the corresponding bromo-compounds using halogen/metal exchange (n-BuLi) and quenching with N,N-dimethylacetamide and dimethylformamide, respectively.

Compounds of the general formula I in which V is -C≡C- may be prepared by reacting an activated derivative of a carboxylic acid of the general formula

$$(Y^1)_m\text{-}(X^1)Ar^1\text{-}COOH$$

with an ethyne derivative

$$H\text{-}C{\equiv}C\text{-}Ar^2(X^2)\text{-}(Y^2)_p$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, Y^2, m, and p refer to the definitions given elsewhere herein.

Reactions of this type are described by Tohda, Y., Sonogashihara, K., Haghara, N., *Synthesis* **1977**, p 777-778. It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride. The reaction is normally carried out using the catalysts described by Tohda, Y. *et al.* cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride. The reaction is suitably carried out in triethylamine, a mixture of triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon. The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30 minutes to 6 hours.

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner, e.g. as described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-Interscience; ISBN: 0471160199; 3nd edition (May 15, 1999). For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar^1 and/or Ar^2 may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether. The protecting group may be removed after the reaction in a manner known *per se*.

The ethyne derivative may be prepared by standard methods, e.g. as described by Nielsen, S. F. Et al., Bioorg. Med. Chem. 6, pp 937-945 (1998). The carboxylic acids may likewise be prepared by standard procedures or by reductive amination as described in the examples.

Compounds of the general formula I in which V is $-CH_2-CH_2-$ can be prepared by ionic hydrogenation of the corresponding α,β-unsaturated compound where V is –CH=CH- as it has been described by the inventors in Nielsen, S.F. et al. Tetrahedron, 53, pp 5573-5580 (1997) and in the examples (see Figure 2).

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed. (especially chapter 15, pages 691-700) and references cited therein. Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones.

Therapeutic uses

The present inventors have found that that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents (see the Examples section). It is of course possible that the compounds also have other interesting properties to be utilised in the medical field.

Thus, the present invention provides, in a further aspect, a compound (chalcone derivative) as defined herein for use as a drug substance, i. e. a medicament.

Moreover, in further aspects the invention relates to the use of the compounds as defined herein for the preparation of a medicament for the treatment of infections, such as infections associated with bacteria, protozoas or *Leishmania spp*.

The invention also provides in still further aspects a method for the treatment of infections such as bacteria, protozoas or *Leishmania spp* in a mammal comprising the administration of the compounds as defined herein to said mammal.

In one aspect, the chalcone derivatives may be used for the treatment of bacterial infections in a mammal in need thereof. Such bacterial infection may be associated with common Gram-positive and/or Gram-negative pathogenes or with microaerophilic or anaerobic bacteria. As a particularly relevant example of bacteria against which chalcone derivatives demonstrates an effect can be mentioned antibiotic-sensitive or -resistant strains of *S.aureus* and/or *E.faecium*. Other examples include community acquired and nosocomial respiratory infections, including *S.pneumoniae*, *S.pyogenes* and members of *Enterobacteriaceae* (e.g. *E.coli*), microaerophilic bacteria associated with gastric disease (e.g. *Helicobacter pylori*) or pathogenic anaerobic bacteria (e.g. *Bacteroides fragilis* and *Clostridium species*).

In still another aspect, the chalcone derivatives as provided herein can be used for the treatment of infections associated with protozoa in a mammal. Examples of infections are those caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*.

In a still further aspect, the chalcone derivatives as defined herein can be used for the treatment of infections in a mammal associated with *Leishmania spp*. Such infections may be cutaneous and/or visceral.

Preliminary results have shown that compounds wherein the Y^1 is the amino-substituent, i. e. m is one and p is 0, in particular positioned the 2-, 3- or 4-position, and preferably positioned in the 2-position, where Ar^1 is phenyl, are particularly promising for the treatment of infections associated with *Leishmania spp*. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, such as where X^2 represent the 2,4 or 2,5 substituents of a phenyl group as Ar^2, appear to be particularly promising. Further, embodiments wherein X^2 represents one or more halogens located in the 2-, 3- and/or 4-position, especially in

the 2- and/or 4-position, optionally in conjunction with an optionally substituted aryl or optionally substituted heteroaryl group in the 3- or 5-position are suitable in this aspect.

Other preliminary results indicate that compounds wherein the Y^1 is the amino-substituent, in particular positioned in the 2-, 3-, or 4-position, preferably in the 2- and/or 4-position, where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by malaria. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted (heteroarylalkyl)amino, optionally substituted (heteroarylalkyl)alkylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, such as where X^2 represent the 2,5 substituents of a phenyl group as Ar^2, appear to be particularly promising. Further, suitable embodiments are those in which X^1 is hydrogen, methoxy or hydroxy. Yet further particularly useful embodiments are those wherein X^2 represents one or two halogen atoms, such as chloro, located in the 2- and/or 4-positions. Another interesting embodiment is the one wherein X^2 represents two substituents, located in the 2- and 5-positions, independently selected from alkoxy, alkyl, aryl, dialkylamino and pyridinylamino, with methoxy being a preferred alkoxy group. When X^2 represents one substituent, especially interesting compounds have X^2 located in the 3- or 4-position, and selected from mono- or di-alkylamino, pyridinylamino, imidazolyl and halogen, the latter being particularly suitable in the 4-position. Typical embodiments wherein X^2 represents three substituents are those wherein these substituents are located in the 2-, 4-, and 5-positions, such as 2-alkoxy, 4-alkoxy, hydroxy or halo, and 5-alkyl or aryl, as well as those wherein the three substituents are located in the 2-, 3-, and 5-positions, such as 2-alkoxy or alkyl, 3-alkoxy or alkyl, and 5-alkoxy or alkyl. In the context of treating infections associated with malaria, further, preferred meanings of R are alkyl, especially methyl.

Additionally, embodiments wherein both m and p are 1 are suitable for treatment of infections associated with malaria. Such embodiments typically have Y^2 in the 2-, 3-, or 5-position.

Embodiments in which m is 0 and p is 1 are currently interesting for the treatment of infections associated with malaria. Those typically have Y^2 in the 2-, 3-, or 4-position when Ar^2 is phenyl. Preferred such compounds are those where Y^2 is located at the 2-position, with further optional presence (X^2) of a 5-aryl substituent. Additionally, typical meanings of X^1 in this context are 2- and/or 4-halo and 2- and/or 4-alkoxy, with 4-methoxy and 2-fluoro being preferred.

Still other preliminary results indicate that compounds wherein the Y^1 is the amino-substituent, in particular positioned in the 2, 3 or 4 position where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by *S. aureus*. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-

alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen appear to be particularly promising.

Formulation of pharmaceutical compositions

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance.

The administration route of the compounds as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic effective concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependent on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same.

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by weight of the total weight of the composition. The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or exipient. Pharmaceutically acceptable carriers or exipients are those known by the person skilled in the art.

Thus, the present invention provides in a further aspect a pharmaceutical composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration. The latter type of compositions are generally known as controlled release formulations.

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations.

Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use.

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No. WO 99/00114, page 29, line 9, to page 40, line 3. Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation. Specific formulations can be found in "Remington's Pharmaceutical Sciences".

Dosages

The compound are preferably administered in an amount of about 0.1-50 mg per kg body weight per day, such as about 0.5-25 mg per kg body weight per day.

For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated.

The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks.

The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months; in particular, the treatment of tuberculosis will normally be carried out for 6-12 months.

The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure.

For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day.

For parenteral administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is convenient. For intravenous administration a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration a dose of about 0.1 mg to about 20 mg per kg body weight per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed.

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable.

In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs. Important aspects of this is the use of the compound against Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another antimalarial drug.

Method of prediction

In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

The method can be performed as described under *DHODH Assay* in the Examples section. It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any compound. Preferably, however, the chemical compound is a chalcone derivative, e.g. a chalcone derivative as defined herein.

EXAMPLES

Preparation of compounds

Chemical names presented below were generated using the software ChemDraw Ultra, version 6.0.1, from CambridgeSoft.com.

The general method for the preparation of the A ring or B ring having the amino-functional group is illustrated in Figure 1.

General procedure A

Preparation of alkyl- or dialkyl aminomethyl acetophenones

To a solution of 2-methyl-[1,3]dioxan-2-yl benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1.5 L) was added sodium triacetoxyborohydride (257mmol) under argon. The resulting suspension was stirred at room temperature for 18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

General procedure B

Preparation of alkyl- or dialkyl aminomethyl benzaldehydes

To a solution of diethoxymethyl benzaldehyde (16.5 mmol) and amine (24.7 mmol) in dry THF (150 mL) was added sodium triacetoxyborohydride (25.7mmol) under argon. The resulting suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification.

General procedure C

Preparation of biaryl carbaldehydes

A solution of Na_2CO_3 (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14.7 mmol) and arylboronic acid (17.6 mmol) in DME (40 mL). The mixture was flushed with argon for 2 minutes followed by addition of $Pd(PPh_3)_2Cl_2$ (310 mg, 3 mol %). The reaction was heated at reflux and left overnight under an atmosphere of argon. The reaction was cooled, 2M Na_2CO_3 was added, and the mixture was extracted with EtOAc (3 x 20 mL). The title products were purified by flash chromatography.

General procedure D

Preparation of amino benzaldehydes

Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), $Pd_2(dba)_3$ (0.2 mmol, 1 mol% Pd), *rac*-BINAP (0.6 mmol) and *t*-BuONa (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 10 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography using 5% Et_3N in EtOAc

General Procedure E

Preparation of aminochalcones with phenolic substituents

To a solution of an acetophenone (2 mmol) and a tetrahydro-pyran-2-yloxy benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added 8M NaOH (0.3 mL), and the mixture was stirred for 3-18 hours at 25°C. The mixture was evaporated on Celite® and the product

was isolated by flash chromatography. The aminochalcone was dissolved in MeOH:Et_2O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH:Et_2O (1:9 v/v) was added. The salt was filtered off. Hydrolysis of the tetrahydropyran ether was carried out by adding H_2O and MeOH and stirring at reflux for 72 hr. The salts of the phenolic aminochalcones were isolated by evaporation. Some aminochalcones did not undergo salt formation, and was isolated as the free base, by extraction from aqueous $NaHCO_3$. The purity was >95% determined by HPLC and the molecular weight was determined by LC-MS.

General procedure F

Preparation of aminochalcones from acetophenones and aldehydes

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added NaOH (0.2 mmol), and the mixture was stirred for 3-18 hours at 25 °C. The mixture was evaporated on Celite® and the product was isolated by flash chromatography. The aminochalcone was dissolved in MeOH:Et_2O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH:Et_2O (1:9 v/v) was added. The salt was filtered off and recrystallised from MeOH or MeCN. Some aminocalcones did not undergo saltformation, and was isolated as the free base. The purity was >95% determined by HPLC.

General procedure G

Preparation of formylchalcones, substituted in the A-ring

A solution of 1-(diethoxymethyl-phenyl)-ethanone (29 mmol), an benzaldehyde (29 mmol), and NaOH (2.9 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et_2O (50 mL) was added and the solution was stirred for 5 hours at 25 °C. H_2O (50 mL) and the mixture was extracted with Et_2O. The organic phases were pooled, dried over Na_2SO_4, and filtered. Evaporation gave the crude title product, which was purified by flash chromatography or crystallization.

General procedure H

Preparation of formylchalcones, substituted in the B-ring

A solution of diethoxymethyl-benzaldehyde (42 mmol), an acetophenone (42 mmol), and sodium hydroxide (8 mmol) in 96% EtOH (100 mL) was stirred for 18 hours at 25 °C. 6M HCl (10 mL) and Et_2O (50 mL) was added and the solution was stirred for 5 hours at 25 °C. H_2O (50 mL) and the mixture was extracted with Et_2O. The organic phases were pooled, dried over Na_2SO_4, and filtered. Evaporation gave the crude title product, which was purified by flash chromatography or crystallization.

General procedure I

Preparation of aminochalcones from formylchalcones

To a solution of an formylchalcone (3.8 mmol) and amine (5.6 mmol) in dry THF (40 mL) was added sodium triacetoxyborohydride (5.6 mmol) under argon. The resulting suspension was stirred at room temperature for 6-18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture extracted with ethyl acetate. The organic phase, was dried over sodium sulphate, filtered, and evaporated on Celite®. The product was isolated by flash chromatography. The purity was >95% determined by HPLC.

Characterisation of the compounds

The compounds were characterised by NMR (300 MHz) and GC-MS/LC-MS.

Acetophenones

1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone

General procedure A gave the title product as brown oil in 78% yield. ^{1}H-NMR ($CDCl_3$,): δ 7.42-7.29 (m, 4H), 3.65 (s, 2H), 2.54 (s, 3H), 2.43 (b, 8H), 2.27 (s, 3H).

1-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-ethanone

General procedure A gave the title product as yellow oil in 18% yield. ^{1}H-NMR ($CDCl_3$): δ 7.91 (d, 2H), 7.42 (d, 2H), 3.85 (s, 2H), 2.68 (t, 2H), 2.60 (s, 3H), 2.36 (t, 2H), 2.22 (s, 6H), 1.73-1.62 (m, 2H).

1-(3-Diethylaminomethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 80% yield. ^{1}H-NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.82 (d, 1H), 7.57 (d, 1H), 7.40 (t, 1H), 3.61 (s, 2H), 2.61 (s, 3H), 2.52 (t, 4H), 1.04 (t, 6H).

1-(3-Dimethylaminomethyl-phenyl)-ethanone

General procedure A gave the title product as yellow oil in 89% yield. ^{1}H-NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.85 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 3.47 (s, 2H), 2.61 (s, 3H), 2.25 (s, 6H).

1-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-ethanone

General procedure A gave the title product as brown oil in 88% yield. ^{1}H-NMR (DMSO) δ 7.51 (d, 1H), 7.40-7.30 (m, 3H), 3.57 (s, 2H), 2.56 (s, 3H), 2.39-2.32 (m, 2H), 2.29-2.23 (m, 2H), 2.07 (s, 6H), 2.03 (s, 3H).

1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-ethanone

General procedure A gave the title product as brown oil in 44% yield. ^{1}H-NMR (DMSO) δ 7.52 (dd, 1H), 7.51 (dd, 1H), 7.40 (td, 1H), 7.30 (td, 1H), 3.63 (s, 2H), 2.48 (s, 3H), 1.91 (s, 3H), 1.03 (s, 9H).

1-[2-(4-Hydroxy-piperidin-1-ylmethyl)-phenyl]-ethanone
General procedure A gave the title product as brown oil in 82% yield. ^{1}H-NMR ($CDCl_3$) δ 7.32 (dt, 1H), 7.28-7.19 (m, 3H), 3.65-3.56 (m, 1H), 3.54 (s, 2H), 2.63-2.55 (m, 2H), 2.45 (s, 3H), 2.10-2.01 (m, 2H), 1.79-1.70 (m, 2H), 1.49-1.36 (m, 2H).

1-(2-Morpholin-4-ylmethyl-phenyl)-ethanone
General procedure A gave the title product as yellow oil in 89% yield. Pure according to GCMS m/z: 219.

1-[4-Hydroxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-ethanone
A solution of formaldehyde (37% w/w, 8.2 mL) was added to a solution of 4'-Hydroxy acetophenone (100 mmol), and *N*-methylpiperazine (110 mmol) in EtOH. Heated at reflux overnight. The solvent was evaporated on celite and the residue was purified by flash chromatography and crystallized from heptane to give the title product as white needles in 55% yield. ^{1}H-NMR (DMSO) δ 7.76 (dd, 1H), 7.74 (s, 1H), 6.81 (d, 1H), 3.69 (s, 2H), 2.47 (br, 4H), 2.46 ((s, 3H), 2.35 (br, 4H), 2.17 (s, 3H).

1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-ethanone
(5-Bromo-2-methoxy-benzyl)-dimethyl-amine (29 mmol), Butoxy-ethene (100 mmol), Palladium acetate (0.9 mmol), 1,3-Bis(diphenylphosphino) propane (1.8 mmol), and potassium carbonate were suspended in DMF (50 ml) and H_2O under argon. Heated at 80 °C overnight. Poured into hydrochloric acid (2 M) and stirred for 1 hour. The mixture was adjusted to basic pH and extracted with CH_2Cl_2. The organic phase was evaporated on celite and the residue was purified by flash chromatography to give the title product as orange oil in 42% yield. ^{1}H-NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.88 (dd, 1H), 6.89 (d, 1H), 3.88 (s, 3H), 3.44 (s, 2H), 2.55 (s, 3H), 2.25 (s, 6H).

Benzaldehydes

2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-benzaldehyde
General procedure B gave the title product as brown oil in 82% yield. ^{1}H-NMR ($CDCl_3$): δ 10.48 (s, 1H), 7,89 (dd, 1H), 7.53-7.24 (m, 3H), 3.87 (s, 2H), 2.55 (t, 2H), 2.44 (t, 2H), 2.23-2.18 (m, 9H).

2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde
General procedure B gave the title product as brown oil in 80% yield. ^{1}H-NMR ($CDCl_3$): δ 10.41 (s, 1H), 7.87 (d, 1H), 7.51 (dt, 1H)7.41 (t, 1H), 7.38 (d, 1H), 3.81 (s, 2H), 2.6-2.3 (m, 8H), 2.27 (s, 3H).

3-Dimethylaminomethyl-4-methoxy-benzaldehyde

To a solution of 4-bromo-2-(dimethylaminomethyl)anisole (12.2 g, 50 mmol) in dry THF (150 mL) at -78°C was added *n*-BuLi (2.5 M, 20 mL, 50 mmol) keeping the temperature below -70°C. The orange mixture was stirred for 15 min and dry DMF (4.7 mL, 60 mmol) was added in one portion. The cooling bath was removed and the light yellow mixture was allowed to warm to 20°C. After 30 min the mixture was hydrolysed with 5% Na_2CO_3 (100 mL), and extracted with Et_2O (3 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure leaving yellow oil (79%) that was pure enough for further reaction. ^{1}H-NMR(DMSO-d_6): δ 9.87 (s, 1H), 7.88-7.40 (m, 1H), 7.81 (d, 1H), 7.19 (d, 1H), 3.88 (s, 3H), 3.42 (s, 2H), 2.17 (s, 6H).

3-(Pyridin-3-ylamino)-benzaldehyde

General procedure D gave the title compound as white crystals in 69% yield.^{1}H-NMR(DMSO-d_6): δ 9.94 (s, 1H), 8.67 (s, 1H), 8.40 (d, 1H), 8.11 (dd, 1H), 7.58-7.50 (m, 2H), 7.47 (d, 1H), 7.43-7.35 (m, 2H), 7.29 (dd, 1H).

3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-benzaldehyde

General procedure B gave the title product as yellow oil in 84% yield. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H), 7.82 (m, 2H), 7.62 (dt, 1H), 7.52 (t, 1H), 3.67 (m, 4H), 2.64 (t, 2H), 2.26 (s, 2H).

3-[(2-Methoxy-ethylamino)-methyl]-benzaldehyde

General procedure B gave the title product as yellow oil in 24% yield. ^{1}H-NMR ($CDCl_3$): δ 10.04, (s, 1H), 7.89 (t, 1H), 7.79 (dt, 1H), 7.65 (dt, 1H), 7.51 (t, 1H), 3.92 (s, 2H), 3.55 (t, 2H), 3.39 (s, 3H), 2.84 (t, 2H), 1.79 (s, 1H).

4-Diethylaminomethyl-benzaldehyde

General procedure B gave the title product as brown oil in 74% yield. ^{1}H-NMR ($CDCl_3$): δ 10.02 (s, 1H), 7.85 (d, 2H), 7.55 (d, 2H), 3.66 (s, 2H), 2.56 (k, 4H), 1.07 (t, 6H).

3-Butylamino-benzaldehyde

General procedure D gave the title compound as yellow oil in 78 % yield. ^{1}H-NMR(DMSO-d_6): δ 9.90 (s, 1H), 7.34 (t, 1H), 7.21 (s, 1H), 7.15-7.05 (m, 2H), 6.96 (dd, 1H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 0.92 (t, 3H).

4-Dibutylamino-2-fluoro-benzaldehyde

General procedure B gave the title product as yellow oil in 56% yield. ^{1}H-NMR ($CDCl_3$): δ 10.02 (s, 1H), 7.68 (t, 1H), 6.23 (d, 1H), 6.18 (d, 1H), 3.29 (t, 4H), 1.71-1.57 (m, 4H), 0.96 (t, 6H).

4-Methoxy-3',5'-dimethyl-biphenyl-3-carbaldehyde

General procedure C gave the title compound as white crystals in 81% yield. ^{1}H-NMR($CDCl_3$): δ 10.41 (s, 1H), 8.00 (d, 1H), 7.68 (dd, 1H), 7.31 (s, 2H), 7.19 (d, 1H), 6.93 (s, 1H),), 4.25 (t, 2H), 2.81 (t, 2H), 2.38 (s, 6H), 2.26 (s, 6H).

3-(Butyl-ethyl-amino)-benzaldehyde

General procedure D gave the title compound as yellow oil in 40 % yield. ^{1}H-NMR(DMSO-d_6): δ 9.90 (s, 1H), 7.35 (t, 1H), 7.12-7.05 (m, 2H), 6.96 (dd, 1H), 3.39 (q, 2H), 3.30 (t, 2H), 1.57-1.42 (m, 2H), 1.40-1.25 (m, 2H), 1.08 (t, 3H), 0.92 (t, 3H).

4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde

2-(2-Chloro-4-methoxy-phenyl)propionitrile:

A solution of 2'-chloro-4'-methoxyacetophenone (18.5 g, 0.10 mol) and tosylmethylisocyanide (TOSMIC, 21.5 g, 0.11 mol) in dry 1,2-dimethoxyethane (100 mL) was cooled to -10°C. A solution of *t*-BuOK (22.4 g, 0.20 mol) in dry *t*-BuOH (250 mL) was added slowly keeping the temperature below 5°C. The homogeneous orange solution was stirred for 2h/0°C and 1h/25°C. The resulting suspension was evaporated to a slurry. Water (200 mL) was added and extracted with Et_2O (3 x 150 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure leaving an orange oil. Yield: 19 g (97%). GCMS: > 98 %; ^{1}H-NMR(DMSO-d_6): δ 7.49 (d, 1H), 7.12 (d, 1H), 7.02 (dd, 1H), 4.42 (q, 1H), 3.80 (s, 3H), 1.55 (d, 3H).

2-(2-Chloro-4-methoxy-phenyl)-2-methyl-propionitrile:

A solution of 2-(2-chloro-4-methoxy-phenyl)propionitrile (19 g, 0.097 mol) and methyliodide (7 mL, 0.11 mol) in dry DMF (100 mL) was flushed with argon for 2 min and cooled to 0°C. Sodium hydride (60% oil susp., 4.4 g, 0.11 mol) was added in small portions. The thick suspension was stirred for another 18h at 25°C and then poured into water (300 mL) and extracted with Et_2O (3 x 100 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure leaving a yellow oil which was distilled. Bp: 103-106°C/0.06 mbar, clear oil that solidifies on standing. Yield: 17.5 g (83%). GCMS: > 99%; ^{1}H-NMR(DMSO-d_6): δ 7.43 (d, 1H), 7.13 (d, 1H), 6.98 (dd, 1H), 3.80 (s, 3H), 1.77 (s, 6H).

2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile:

A solution of 2-(2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.0835 mol) in TFA (100 mL) was cooled to 0°C. N-bromosuccinimide (14.9 g, 0.0835 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 13 g (54%). GCMS: > 99% ^{1}H-NMR(DMSO-d_6): δ 7.56 (s, 1H), 7.23 (s, 1H), 3.84 (s, 3H), 1.70 (s, 6H).

2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde:

A solution of 2-(5-bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionitrile (13 g, 0.045 mol) in dry THF (80 mL) was cooled to -10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure. The aqueous phase was cooled and the crude product was filtered off and recrystallized from boiling MeOH. Yield: 7.8 g (59%). GCMS: > 99%; ^{1}H-NMR(DMSO-d_6): δ 9.61 (s, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 3.89 (s, 3H), 1.40 (s, 6H).

1-Bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene:
A suspension of methyltriphenylphosphonium bromide (11.4 g, 0.032 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 12 mL, 0.030 mol) was added slowly. The suspension became more homogenous. The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C. 2-(5-Bromo-2-chloro-4-methoxy-phenyl)-2-methyl-propionaldehyde (7.8 g, 0.027 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.92 g (50%). GCMS: > 99%; ^{1}H-NMR(DMSO-d_6): δ 7.55 (s, 1H), 7.14 (s, 1H), 6.05 (dd, 1H), 5.04 (dd, 1H), 4.92 (dd, 1H), 3.87 (s, 3H), 1.45 (s, 6H).
4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzaldehyde:
To a solution of 1-bromo-4-chloro-5-(1,1-dimethyl-allyl)-2-methoxy-benzene (3.92 g, 0.0135 mol) in dry THF (30 mL) was cooled to −78°C under argon. *n*-BuLi (2.5M, 6 mL, 0.0145 mol) was added keeping the temperature below −70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.2 mL, 0.015 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of $NaHCO_3$ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was recrystallized from MeOH. Yield: 3.00 g (93%). GCMS: > 99%; ^{1}H-NMR(DMSO-d_6): δ 10.30 (s, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 6.08 (dd, 1H), 5.06 (dd, 1H), 4.91 (dd, 1H), 3.93 (s, 3H), 1.49 (s, 6H).

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde
2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile:
A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17.5 g, 0.10 mol) in TFA (80 mL) was cooled to 0°C. N-bromosuccinimide (17.8 g, 0.10 mol) was added in small portions keeping the temperature below 5°C. The orange solution was stirred for 2h/25°C and evaporated to dryness. Water (200 mL) was added and the mixture was stirred vigorously for 1 h. The crude product was filtered off and recrystallized from boiling MeOH. The pure product was isolated as white needles. Yield: 19.3 g (76%). GCMS: > 99%; ^{1}H-NMR(DMSO-d_6): δ 7.68 (d, 1H), 7.50 (dd, 1H), 7.16 (d, 1H), 3.86 (s, 3H), 1.70 (s, 6H).
2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde:
A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12.71 g, 0.050 mol) in dry THF (100 mL) was cooled to −10°C under argon. DIBALH (1M in THF, 100 mL, 0.10 mol) was added keeping the temperature below 0°C. The mixture was stirred for 30 min/0°C and then 2 h/25°C. The clear solution was carefully poured into icecold hydrochloric acid (2M, 100 mL). The THF was removed under reduced pressure to give clear oil. The oil was destilled (b.p. 114-130 °C/ 4.3 x 10^{-3} mbar) Yield: 7.40 g (58%). GCMS: > 99%; ^{1}H-NMR($CDCl_3$): δ 9.44 (s, 1H), 7.45 (d, 1H), 7.15 (dd, 1H), 6.90 (d, 1H), 3.89 (s, 3H), 1.43 (s, 6H).
2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene:
A suspension of methyltriphenylphosphonium bromide (7.71 g, 0.0215 mol) in dry THF (100 mL) was cooled to 0°C under argon. *n*-BuLi (2.5M, 8 mL, 0.020 mol) was added slowly. The resulting clear orange solution of the ylide was stirred for another 15 min at

0°C. 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3.7 g, 0.014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution. The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using *n*-heptane as eluent. Yield: 3.1 g (84%). GCMS: > 99%; ^{1}H-NMR($CDCl_3$): δ 7.50 (d, 1H), 7.23 (dd, 1H), 6.83 (d, 1H), 5.97 (dd, 1H), 5.06 (dd, 1H), 5.02 (dd, 1H), 3.87 (s, 3H), 1.44 (s, 6H).

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde:

To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3.1 g, 0.012 mol) in dry THF (50 mL) was cooled to -78°C under argon. *n*-BuLi (2.5M, 5.1 mL, 0.0128 mol) was added keeping the temperature below -70°C. The yellow mixture was stirred for another 15 min and quenched with dry DMF (1.4 mL, 0.018 mol). The cooling bath was removed and the mixture was allowed to warm to 25°C. A saturated solution of $NaHCO_3$ (30 mL) was added and then extracted with EtOAc (3 x 50 mL). The organic phase was dried (Na_2SO_4) and evaporated to yellow oil. Yield: 2.31 g (94%). ^{1}H-NMR($CDCl_3$): δ 10.48 (s, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 6.94 (d, 1H), 6.00 (dd, 1H), 5.05 (dd, 1H), 5.01 (dd, 1H), 3.93 (s, 3H), 1.41 (s, 6H).

3-Morpholin-4-ylmethyl-benzaldehyde

General procedure B gave the title product as yellow oil in 71% yield. ^{1}H-NMR ($CDCl_3$): δ 10.05 (s, 1H), 7.88 (s, 1H), 7.81 (d, 1H), 7.64 (d, 1H), 7.51 (t, 1H), 3.74 (t, 4H), 3.58 (s, 2H), 2.48 (t, 4H).

2-Methoxy-5-(pyridin-3-ylamino)-benzaldehyde

General procedure D gave the title product as yellow oil that precipitated on standing in 39% yield. ^{1}H-NMR ($CDCl_3$): δ 10.42 (s, 1H), 8.27 (d, 1H), 8.08 (dd, 1H), 7.55 (d, 1H), 7.33 (dd, 1H), 7.26 (ddd, 1H), 7.11 (dd, 1H), 6.95 (d, 1H), 6.34 (bs, 1H), 3.90 (s, 3H).

4-Dimethylaminomethyl-biphenyl-3-carbaldehyde

Biphenyl-4-ylmethyl-dimethyl-amine (55 mmol) was dissolved in diethyl ether and a solution of n-BuLi (65 mmol) was added. Heated at reflux for 6 hours under argon. The solution was cooled on ice-bath, before DMF (60 mmol) was added. Stirred overnight. Aqueous work-up and vacuum destillation (b.p. 130-145 °C/0.015 mbar) gave the title product as yellow oil in 40 % yield. ^{1}H-NMR (DMSO) δ 10.38 (s, 1H), 8.03 (d, 1H), 7.89 (dd, 1H), 7.73-7.69 (m, 2H), 7.53-7.39 (m, 4H), 3.76 (s, 2H), 2.17 (s, 6H).

3',5'-Dichloro-4,6-dimethoxy-biphenyl-3-carbaldehyde

General procedure C gave the title product as beige powder in 54% yield. ^{1}H-NMR (DMSO) δ 10.22 (s, 1H), 7.62 (s, 1H), 7.55 (t, 1H), 7.48 (d, 2H), 6.87 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H).

3-(Pyridin-4-ylamino)-benzaldehyde

General procedure D gave the title product as brown crystals in 11% yield. ^{1}H-NMR (d_6-DMSO): 9.99 (s, 1H), 9.07 (s, 1H), 8.25 (d, 2H), 7.78 (s, 1H), 7.57-7.51 (m, 3H), 6.97 (d, 2H).

3-[(Pyridin-3-ylmethyl)-amino]-benzaldehyde
General procedure D gave the title product as brown crystals in 87% yield. ^{1}H-NMR (d_6-DMSO): 9.85 (s, 1H), 8.61 (d, 1H), 8.45 (dd ,1H), 7.76 (dt, 1H), 7.35 (dd, 1H), 7.29 (t, 1H), 7.11-7.08 (m, 2H), 6.95 (dd, 1H), 6.71 (t, 1H), 4.37 (d, 2H).

Formylchalcones

***(E)*-2-[3-(2-Bromo-phenyl)-3-oxo-propenyl]-benzaldehyde**
General procedure H gave the title product as yellow crystals in 47% yield. ^{1}H-NMR ($CDCl_3$): δ 10.21 (s, 1H), 8.24 (d, 1H), 7.86 (dd, 1H), 7.73 (dd, 1H), 7.67-7.57 (m, 3H), 7.50 (dd, 1H), 7.45 (td, 1H), 7.35 (td, 1H), 7.00 (d, 1H).

***(E)*-3-[3-(4-Methoxy-phenyl)-3-oxo-propenyl]-benzaldehyde**
General procedure H gave the title compound as white crystals in 53% yield. ^{1}H NMR ($CDCl_3$): δ 10.08 (s, 1H), 8.42 (bs, 1H), 8.2 (m, 3H), 8.07 (d, 1H), 7.88 (dt, 1H), 7.78 (d, 1H), 7.69 (t, 1H), 7.11 (d, 2H), 3.88 (s, 3H).

***(E)*-4-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde**
General procedure G gave the title compound as white crystals in 7% yield. ^{1}H NMR ($CDCl_3$): δ 10.13 (s, 1H), 8.15 (m, 3H), 8.02 (d, 2H), 7.70 (d, 1H), 7.49 (d, 1H), 7.46 (d, 1H), 7.33 (dd, 1H).

***(E)*-3-[3-(2,4-Dichloro-phenyl)-acryloyl]-benzaldehyde**
General procedure G gave the title products as a white solid in 7 % yield. ^{1}H-NMR($CDCl_3$): δ 10.12 (s, 1H), 8.5 (t, 1H), 8.32-8.26 (m, 1H), 8.18 (d, 1H), 8.15-8.10 (m, 1H), 7.72 (d, 1H), 7.72 (s, 1H), 7.54-7.48 (m, 2H), 7.36-7.30 (m, 1H).

Aminochalcones

A001: *(E)*- 1-(4-Methoxy-phenyl)-3-(4-morpholin-4-ylmethyl-phenyl)-propenone
General procedure I gave the fumaric acid salt of the title compound as slightly yellow crystals in 16% yield. ^{1}H-NMR(DMSO-d_6): δ 8.15 (d, 2H), 7.91 (d, 1H), 7.83 (d, 2H), 7.69 (d, 1H), 7.39 (d, 2H), 7.08 (d, 2H), 6.63 (s, 2H), 3.86 (s, 3H), 3.59 (t, 4H), 3.52 (s, 2H), 2.40 (t, 4H).

A002: *(E)*- 3-(4-Diethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone
General procedure I gave fumaric acid salt of the title compound as slightly yellow crystals in 25% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.92 (d, 1H), 7.84 (d, 2H), 7.69 (d, 1H), 7.43 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.75 (s, 2H), 2.61 (q, 4H), 1.05 (t, 6H).

A003: *(E)*- 1-(4-Methoxy-phenyl)-3-(4-propylaminomethyl-phenyl)-propenone
General procedure I gave fumaric acid salt of the title compound as white crystals in 59% yield. ^{1}H-NMR(DMSO-d_6): δ 8.17 (d, 2H), 7.95 (d, 1H), 7.88 (d, 2H), 7.70 (d, 1H), 7.51 (d,

2H), 7.09 (d, 2H), 6.51 (s, 2H), 3.96 (s, 2H), 3.87 (s, 3H), 2.70-2.61 (m, 2H), 1.60-1.49 (m, 2H), 0.88 (s, 3H).

A004: *(E)*- 3-(4-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave fumaric acid salt of the title compound as off-white crystals in 60% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.93 (d, 1H), 7.83 (d, 2H), 7.70 (d, 1H), 7.41 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.88 (s, 3H), 3.60 (s, 2H), 2.28 (s, 6H).

A005: *(E)*-3-{4-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 27% yield. ^{1}H-NMR(DMSO-d_6): δ 8.17 (d, 2H), 7.94 (d, 1H), 7.86 (d, 2H), 7.70 (d, 1H), 7.48 (d, 2H), 7.09 (d, 2H), 6.53 (s, 2H), 3.90 (s, 2H), 3.88 (s, 3H), 2.79 (t, 2H), 2.63 (t, 2H), 2.31 (s, 6H).

A006: *(E)*- 1-(4-Methoxy-phenyl)-3-(4-piperidin-1-ylmethyl-phenyl)-propenone

General procedure I gave the title compound as yellow crystals in 79% yield. ^{1}H-NMR($CDCl_3$): δ 8.04 (d, 2H), 7.90 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.37 (d, 2H), 6.98 (d, 2H), 3.87 (s, 3H), 3.50 (s, 2H), 2.39 (br, 4H), 1.62-1.52 (m, 4H), 1.49-1.40 (m, 2H).

A007: *(E)*- 3-{4-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 23% yield. ^{1}H-NMR(DMSO-d_6): δ 8.17 (d, 2H), 7.94 (d, 1H), 7.87 (d, 2H), 7.70 (d, 1H), 7.49 (d, 2H), 7.09 (d, 2H), 6.49 (s, 2H), 3.92 (s, 2H), 3.88 (s, 3H), 2.71 (t, 2H), 2.46 (t, 2H), 2.23 (s, 6H), 1.88-1.65 (m, 2H).

A008: *(E)*- 3-(4-Dibutylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave the title compound as yellow crystals in 62% yield. ^{1}H-NMR($CDCl_3$): δ 8.04 (d, 2H), 7.80 (d, 1H), 7.58 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.40 (t, 4H), 1.49-1.40 (m, 4H), 1.36-1.20 (m, 4H), 0.88 (t, 6H).

A009: (*E*)- 3-{4-[(4-Diethylamino-1-methyl-butylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the title compound as brown oil in 24% yield. ^{1}H-NMR($CDCl_3$): δ 8.04 (d, 2H), 7.80 (d, 1H), 7.59 (d, 2H), 7.52 (d, 1H), 7.38 (d, 2H), 6.98 (d, 2H), 3.90 (s, 3H), 3.57 (s, 2H), 2.79-2.61 (m, 1H), 2.60-2.50 (q, 4H), 2.49-2.40 (t, 2H), 1.52-1.48 (m, 2H), 1.38-1.23(m, 2H), 1.06 (d, 3H), 1.01 (t, 6H).

A010: (*E*)- 3-{3-[(2-Dimethylamino-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 43% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.95 (s, 1H), 7.93 (d, 1H), 7.81 (d, 1H),

7.70 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.58 (s, 2H), 3.95 (s, 2H), 3.88 (s, 3H), 2.85 (t, 2H), 2.70 (t, 2H), 2.35 (s, 6H).

A011: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 72% yield. ^{1}H-NMR(DMSO-d_6): δ 8.26 (d, 1H), 8.15 (d, 2H), 8.04 (d, 1H), 7.96 (d, 1H), 7.78 (d, 1H), 7.56 (dd, 1H), 7.52 (d, 2H), 6.60 (s, 2H), 3.60 (s, 2H), 2.22 (s, 6H).

A012: (*E*)- 1-(4-Methoxy-phenyl)-3-(3-propylaminomethyl-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 28% yield.^{1}H-NMR(DMSO-d_6): δ 8.15 (d, 2H), 7.98 (s, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52-7.43 (m, 2H), 7.10 (d, 2H), 6.52 (s, 2H), 3.99 (s, 2H), 3.86 (s, 3H), 2.69 (t, 2H), 1.62-1.50 (m, 2H), 0.89 (t, 3H).

A013: (*E*)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 43% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 6.99 (d, 2H), 6.59 (s, 2H), 3.87 (s, 3H), 3.55 (s, 2H), 2.70-2.55 (br, 4H), 2.54-2.45 (br, 4H), 2.35 (s, 3H).

A014: (*E*)- 1-(4-Methoxy-phenyl)-3-[3-(4-methyl-[1,4]diazepan-1-ylmethyl)-phenyl]-propenone

General procedure I gave the fumaric acid salt of the title compound as off-white crystals in 70% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.70 (d, 1H), 7.45-7.40 (m, 2H), 7.09 (d, 2H), 6.57 (s, 2H), 3.87 (s, 3H), 3.69 (s, 2H), 3.08-3.00 (m, 2H), 2.99-2.97 (m, 2H), 2.80-2.75 (m, 2H), 2.72-2.65 (m, 2H), 2.58 (s, 3H), 1.90-1.81 (m, 2H).

A015: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 23% yield. ^{1}H-NMR(DMSO-d_6): δ 8.16 (d, 2H), 7.92 (d, 1H), 7.80-7.75 (m, 2H), 7.69 (d, 1H), 7.45-7.37 (m, 2H), 7.09 (d, 2H), 6.60 (s, 2H), 3.87 (s, 3H), 3.51 (s, 2H), 2.21 (s, 6H).

A016: (*E*)- 1-(2-Bromo-phenyl)-3-(2-dimethylaminomethyl-phenyl)-propenone

General procedure I gave the title compound as slightly green crystals in 17% yield. ^{1}H-NMR($CDCl_3$): δ 7.96 (d, 1H), 7.72-7.67 (m, 1H), 7.64 (dd, 1H), 7.44-7.37 (m, 2H), 7.36-7.29 (m, 3H), 7.25-7.21 (m, 1H), 6.95 (d, 1H), 3.35 (s, 2H), 2.07 (s, 6H).

A017: (*E*)- 3-{3-[(3-Dimethylamino-propylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the title compound as yellow oil in 27% yield. ^{1}H-NMR($CDCl_3$): δ 8.06 (d, 2H), 7.80 (d, 1H), 7.65-7.50 (m, 3H), 7.40-7.37 (m, 2H), 6.99 (d, 2H), 3.90 (s, 3H), 3.84 (s, 2H), 2.70 (t, 2H), 2.35 (t, 2H), 2.20 (s, 6H), 1.70-1.60 (m, 2H).

A018: (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 64% yield. ^{1}H-NMR(DMSO-d_6): δ 7.99 (d, 2H), 7.90 (d, 1H), 7.78 (d, 1H), 7.45-7.30 (m, 3H), 6.90 (s, 2H), 6.45 (s, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 3.45 (s, 3H), 2.21 (s, 6H).

A019: (*E*)- 3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as orange oil in 24% yield. ^{1}H-NMR($CDCl_3$): δ 7.91 (d, 2H), 7.84 (d, 1H), 7.75-7.41 (m, 4H), 7.32 (d, 1H), 6.62 (d, 2H), 3.58 (s, 2H), 3.32 (t, 4H), 2.26 (s, 6H), 1.64-1.54 (m, 4H), 1.46-29 (m, 4H), 0.97 (t, 6H).

A020: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as white powder in 29% yield. ^{1}H-NMR(DMSO-d_6): δ 8.27 (d, 1H), 8.15-8.07 (m, 2H), 8.02 (d, 1H), 7.95 (d, 1H), 7.77 (d, 1H), 7.65 (d, 1H), 7.60-7.52 (m, 2H), 6.60 (s, 2H), 3.65 (s, 2H), 2.28 (s, 6H).

A021: (*E*)- 3-(2,4-Dichloro-phenyl)-1-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure I gave the fumaric acid salt of the title compound as white powder in 33% yield. ^{1}H-NMR(DMSO-d_6): δ 8.04 (d, 1H), 7.87 (d, 1H), 7.84-7.69 (m, 3H), 7.55 (d, 1H), 7.43-7.29 (m, 3H), 6.60 (s, 4H), 3.61 (s, 2H), 2.70-2.55 (br, 4H), 2.50-2.40 (br, 4H), 2.35 (s, 3H).

A022: (*E*)- 3-(2,4-Dichloro-phenyl)-1-{3-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

General procedure I gave the fumaric acid salt of the title compound as white powder in 8% yield. ^{1}H-NMR(DMSO-d_6): δ 8.26-8.23 (m, 2H), 8.13 (br d, 1H), 8.03 (d, 1H), 7.96 (d, 1H), 7.77 (d, 1H), 7.74 (br d, 1H), 7.62-7.55 (m, 2H), 6.53 (s, 4H), 4.05 (s, 2H), 2.78 (t, 2H), 2.59 (t, 2H), 2.34 (s, 6H), 1.78 (p, 2H).

A023: (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-{4-[(3-dimethylamino-propylamino)-methyl]-phenyl}-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 9% yield. ^{1}H-NMR(DMSO-d_6): δ 8.15 (d, 2H), 8.04 (d, 1H), 7.90 (d, 1H), 7.64 (d, 2H), 7.56 (t, 1H), 7.04 (d, 2H), 6.53 (s, 4H), 4.07 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.81 (t, 2H), 2.74 (t, 2H), 2.45 (s, 6H), 1.86 (p, 2H).

A024: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 60% yield. ^{1}H-NMR(DMSO-d_6): δ 7.84 (t, 1H), 7.69 (br, 2 H), 7.65 (d, 1H), 7.49 (dd, 1H), 7.43 – 7.40 (m, 2H), 6.97 (dd, 1H), 6.96 (t, 1H), 6.60 (s, 2H), 3.88 (s, 3H), 3.52 (s, 2H), 2.21 (s, 6H).

A025: (*E*)- 3-(4-Dibutylamino-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as orange crystals in 2% yield. ^{1}H-NMR(DMSO-d_6): δ 8.05 (d, 2H), 7.67-7.54 (m, 4H), 7.46 (d, 2H), 6.68 (d, 2H), 6.59 (s, 4H), 3.59 (s, 2H), 3.34 (t, 4H), 2.71 (br, 4H), 2.41 (s, 3H,), 1.52-1.47 (m, 4H), 1.39-1.27 (m, 4H), 0.92 (t, 6H).

A026: (*E*)- 3-(2,4-Dichloro-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 50% yield. ^{1}H-NMR(DMSO-d_6): δ 8.06 (d, 1H), 7.71- 7.70 (m, 1H), 7.52- 7.39 (m, 6H), 7.30 (d, 1H), 6.56 (s, 4H), 3.61 (s, 2H), 2.49 (br, under DMSO, 4H), 2.35 (br, 4H), 2.27 (s, 3H).

A027: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 31% yield. ^{1}H-NMR(DMSO-d_6): δ 8.10 (d, 1H), 7.71 (d, 1H), 7.62- 7.59 (m, 2H), 7.55 – 7.39 (m, 6H), 6.59 (s, 2H), 3.73 (s, 2H), 2.19 (s, 6H).

A028: (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as brown oil in 69% yield. ^{1}H-NMR($CDCl_3$): δ 7.51 (d, 2H), 7.41-7.27 (m, 3H), 7.08-7.03 (m, 2H), 6.93 – 6.82 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.75 (s, 2H), 2.38-2.19 (br, 8H), 2.19 (s, 3H).

A029: (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as brown oil in 82% yield. ^{1}H-NMR($CDCl_3$): δ 7.58 (d, 1H), 7.43-7.32 (m, 4H), 7.13-7.07 (m, 2H), 6.95 – 6.83 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.56 (s, 2H), 2.19 (s, 6H).

A030: (*E*)- 3-(4-Dibutylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as brown oil in 49% yield. ^{1}H-NMR($CDCl_3$): δ 7.46 (d, 1H), 7.42-7.28 (m, 5H), 7.21 (d, 1H), 6.85 (d, 1H), 6.59 (d, 2H), 3.53 (s, 2 H), 3.30 (t, 4H), 2.16 (s, 6H), 1.61-1.53 (m, 4H), 1.40-1.35 (m, 4H), 0.96 (t, 6H).

A031: (*E*)- 3-(4-Dibutylamino-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as orange oil in 71% yield. ^{1}H-NMR($CDCl_3$): δ 7.38-7.28 (m, 6H), 7.18 (d, 1H), 6.82 (d, 1H), 6.59 (d, 2H), 3.60 (s, 2H), 3.30 (t, 4H), 2.39-2.26 (br, 8H), 2.19 (s, 3H), 1.63-1.53 (m, 4H), 1.40-1.30 (m, 4H).

A032: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-pyridin-2-yl-propenone

General procedure I gave the fumaric acid salt of the title compound as white crystals in 30% yield. ^{1}H-NMR(DMSO-d_6): δ 8.82 (d, 1H), 8.28 (d, 1H), 8.14-8.03 (m, 2H), 7.87 (d, 1H), 7.79-7.69 (m, 2H), 7.56-7.43 (m, 2H), 7.11-7.04 (m 1H), 6.60 (s, 2H), 3.58 (s, 2H), 2.25 (s, 6H).

A033: (*E*)- 3-(4-Dibutylamino-phenyl)-1-(4-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as orange oil in 28% yield. ^{1}H-NMR($CDCl_3$): δ 7.98 (d, 2H), 7.79 (d, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.33 (d, 1H), 6.64 (d, 2H), 6.63 (s, 2H), 4.14 (q, 4H), 2.28 (s, 6H), 1.66-1.57 (m, 4H), 1.45-1.38 (m, 4H), 0.99 (t, 6H).

A034: (*E*)- 3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as yellow oil in 26% yield. ^{1}H-NMR($CDCl_3$): δ 7.58 (d, 1H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.15 8d, 1H), 6.86 (d, 1H), 6.01 (dd, 1H), 5.10-5.04 (m, 2H), 3.83 (s, 3H), 3.57 (s, 2H), 2.16 (s, 6H), 1.41 (s, 6H).

A035: (*E*)- 1-{2-[(tert-Butyl-methyl-amino)-methyl]-phenyl}-3-(2,4-dichloro-phenyl)-propenone

General procedure F gave the title compound as orange oil in 33% yield. ^{1}H-NMR($CDCl_3$): δ 7.48-7.12 (m 8H), 6.82 (d, 1H), 3.57 (s, 2H), 1.81 (s, 3H), 0.90 (s, 9H).

A036: (*E*)- Acetic acid 1-{2-[3-(2,4-dichloro-phenyl)-acryloyl]-benzyl}-piperidin-4-yl ester

General procedure F gave the title compound as orange oil in 45% yield. ^{1}H-NMR($CDCl_3$): δ 7.60 (d, 1H), 7.48 (d, 1H), 7.45-7.29 (m, 6H), 6.97 (d, 1H), 4.74-4.68 (m, 1H), 3.61 (s, 2H), 2.61-2.54 (m, 2H), 2.25-2.17 (m, 2H), 2.02 (s. 3H), 1.77- 1.71 (m, 2H), 1.62-1.49 (m, 2H).

A037: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-morpholin-4-ylmethyl-phenyl)-propenone

General procedure F gave the title compound as yellow oil in 38% yield. ^{1}H-NMR($CDCl_3$): δ 7.62 (d, 1H, 7.565 (d, 1H), 7.54- 7.30 (m, 6H), 6.99 (d, 1H), 3.62 (s, 2H), 3.55 (t, 4H), 2.37 (t, 4H).

A038: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-propenone
General procedure F gave the title compound as orange oil in 10% yield. ^{1}H-NMR($CDCl_3$): δ 7.63 (d, 1H), 7.58 (d, 1H), 7.45-7.29 (m, 6H), 6.99 (d, 1H), 3. 67 (s, 2H), 2.49-2.44 (m 2H), 2.35-2.30 (m, 2H), 2.16 (s, 6H), 2.11 (s, 3H).

A039: (*E*)-3-(4-Diethylaminomethyl-phenyl)-1-o-tolyl-propenone
General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 32% yield. ^{1}H-NMR(DMSO): δ 7.77 (d, 2H), 7.62 (dd, 1H), 7.49-7.32 (m, 7H), 6.60 (s, 3H), 3.79 (s, 2H), 2.64 (q, 4H), 2.38 (s, 3H), 1.05 (t, 6H).

A040: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-methoxy-phenyl)-propenone
General procedure F gave the title compound as orange oil in 22% yield. ^{1}H-NMR($CDCl_3$): δ 7.52 (d, 1H), 7.51 (dd, 1H), 7.44-7.37 (m, 3H), 7.28-7.26 (m 2H), 7.27 (d, 1H), 6.99-6.91 (m, 2H), 3,82 (s, 3H), 3.37 (s, 2H), 2.18 (s, 6H).

A041: (*E*)- 3-(4-Chloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the fumaric acid salt of the title compound as white crystals in 22% yield. ^{1}H-NMR(DMSO): δ 7.80 (d, 2H), 7.59 (d, 1H), 7.55-7.41 (m, 5H), 7.37 (s, 2H), 6.60 (s, 2H), 3.71 (s, 2H), 2.19 (s, 6H).

A042: (*E*)- 3-(2,4-Difluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the fumaric acid salt of the title compound as white crystals in 46% yield. ^{1}H-NMR(DMSO): δ 8.09-8.02 (m, 1H), 7.55-7.19 (m, 7H), 7.17-7.16 (m, 1H), 6.60 (s, 2H), 3.66 (s, 2H), 2.15 (s, 6H).

A043: (*E*)- 3-(3-Butylamino-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the title compound as brown oil in 34% yield. ^{1}H-NMR ($CDCl_3$): δ 7.45-7.32 (m, 4H), 7.21-7.16 (m, 1H), 7.17 (d, 1H), 7.01 (d, 1H), 6.87 (d, 1H), 6.74 (t, 1H), 6.64 (dd, 1H), 3.69 (br, 1H), 3.60 (s, 2H), 3.14 (t, 2H), 2.15 (s, 6H), 1.68-1.61 (m, 2H), 1.49-1.39 (m, 2H), 0.98 (t, 3H).

A044: (*E*)- 3-(4-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the title compound as brown oil in 20% yield. ^{1}H-NMR($CDCl_3$): δ 7.46 (d, 2H), 7.41-7.20 (m, 7H), 7.03 (d, 1H), 3.57 (s, 2H), 3.53 (s, 2H), 2.52 (q, 4H), 2.13 (s, 6H), 1.04 (t, 6H).

A045: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-diethylaminomethyl-phenyl)-propenone
General procedure F gave the fumaric acid salt of the title compound as white powder in 28% yield. ^{1}H-NMR (DMSO): δ 13.07 (br, 1H), 8.08 (d, 1H), 7.72 (d, 1H), 7.54-7.37 (m, 6H), 7.32 (d, 1H), 6.61 (s, 2H), 3.72 (s, 2H), 2.40 (q, 4H), 0.85 (t, 6H).

A046: (*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 5% yield. ^{1}H-NMR (DMSO) δ 8.11 (d, 2H), 8.03 (d, 1H), 7.96 (d, 1H), 7.55-7.54 (m, 1H), 7.50 (d, 2H), 7.06-7.05 (m, 2H), 6.59 (s, 4H), 3.85 (s, 3H), 3.80 (s, 3H), 3.60 (s, 2H), 2.65 (br, 4H), 2.56-2.49 (under DMSO, 2H), 2.37 (s, 3H).

A047: (*E*)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-hydroxy-2-methoxy-5-propyl-phenyl)-propenone

General procedure F, using acidic work-up, gave the title compound as red oil in 20% yield. ^{1}H-NMR (DMSO) δ 10.23 (br, 1H), 7.65 (d, 1H), 7.60-7.47 (m, 5H), 7.17 (d, 1H), 6.62 (s, 1H), 3.88 (s, 3H), 3.61 (s, 2H), 2.59 (t, 2H), 2.18 (s, 6H), 1.73-1.63 (m, 2H), 1.01 (t, 3H).

A048: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 27% yield. ^{1}H-NMR (DMSO) δ 8.08 (d, 1H), 7.72 (d, 1H), 7.53-7.40 (m, 6H), 7.40 (d, 1H), 6.45 (s, 2H), 3.64 (s, 2H), 2.8 (br, 4H), 2.4 (br, 4H).

A049: (*E*)-3-(2,5-Dimethoxy-phenyl)-1-(2-piperazin-1-ylmethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 30% yield. ^{1}H-NMR (DMSO) δ 10.37 (br, 2H), 7.53 (d, 1H), 7.44-7.33 (m, 5H), 7.25 (d, 1H), 7.00 (d, 2H), 6.44 (s, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.59 (s, 2H), 2.78 (br, 4H), 2.37 (br, 4H).

A050: (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-fluoro-phenyl)-propenone

General procedure F gave the title compound as brown oil in 39% yield. ^{1}H-NMR($CDCl_3$): δ 7.54-7.27 (m, 6H), 6.85 (d, 1H), 6.32 (dd, 1H), 6.18 (dd, 1H), 3.47 (s, 2H), 3.18 (t, 4H), 2.08 (s, 6H), 1.61-1.49 (m, 4 H), 0.87 (t, 6H).

A051: (*E*)-3-(2,4-Dichloro-phenyl)-1-[2-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as brown semi-solid in 39% yield. ^{1}H-NMR (DMSO) δ 8.05 (d, 1H), 7.70 (d, 1H), 7.50-7.25 (m, 7H), 4.46 (br, 1H), 3.55 (s, 2H), 3.35-3.32 (m, 2H), 2.47-2.44 (m, 2H (under DMSO)), 2.00-1.93 (m, 2H), 1.53-1.49 (m, 2H), 1.24-1.21 (m, 2H).

A052: (*E*)-1-(3-Diethylaminomethyl-phenyl)-3-(2,5-dimethoxy-phenyl)-propenone

General procedure F gave the title compound as yellow oil in 41% yield. ^{1}H-NMR (DMSO) δ 8.07 (d, 1H), 7.95 (s, 1H), 7.87 (d, 1H), 7.59 (d, 1H), 7.58 (d, 1H), 7.44 (t, 1H), 7.18 (d, 1H), 6.94 (dd, 1H), 6.88 (d, 1H), 3.87 (s, 3H), 2.82 (s, 3H), 3.60 (s, 2H), 2.55 (q, 4H), 1.06 (t, 6H).

A053: (*E*)- 3-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 39% yield. ^{1}H-NMR (DMSO) δ 7.71-7.68 (m, 1H), 7.50 (d, 1H), 7.27-7.11 (m, 7H), 6.86 (d, 1H), 6.34 (s, 4H), 3.38 (s, 2H), 3.27 (s, 2H), 2.40 (t, 2H), 2.24 (t, 2H), 2.15 (s, 6H), 2.11 (br, 4H), 1.94 (s, 3H), 1.79 (s, 3H).

A054: (*E*)- 3-(2,4-Dimethoxy-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 48% yield. ^{1}H-NMR (DMSO) δ 7.46 (d, 1H), 7.25 (d, 1H9, 7.19-7.12 (m, 5H), 6.82 (d, 1H), 6.38-6.33 (m, 2H), 6.36 (s, 4H), 3.58 (s, 3H), 3.58 (s, 3H), 3.30 (s, 2H), 2.25 (br, 4H), 1.94 (s, 3H).

A055: (*E*)-3-(4-Imidazol-1-yl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 46% yield.^{1}H-NMR (DMSO) δ 8.38 (t, 1H), 7.91 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.44-7.31 (m, 6H), 7.14 (t, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.34 (br, 8H), 2.19 (s, 3H).

A056: (*E*)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-2-yl-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 58% yield. ^{1}H-NMR (DMSO) δ 8.64 (d, 1H), 8.85 (td, 1H), 7.76 (d, 1H), 7.48-7.37 (m, 6H), 7.19 (d, 1H), 6.68 (s, 2H), 3.55 (s, 2H), 2.29 (br, 8H), 2.13 (s, 3H).

A057: (*E*)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-3-yl-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 19% yield. ^{1}H-NMR (DMSO) δ 8.88 (d, 1H), 8.58 (dd, 1H), 8.21 (d, 1H), 7.48-7.39 (m, 5H), 7.37 (d, 1H), 7.29 (d, 1H), 6.59 (s, 4H), 3.60 (s, 2H), 2.41 (br, 4H), 2.33 (br, 4H), 2.21 (s, 3H).

A058: (*E*)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-pyridin-4-yl-propenone

General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 6% yield. ^{1}H-NMR (DMSO) δ 8.61 (d, 2H), 7.70 (d, 2H), 7.47-7.40 (m, 5H), 7.20 (d, 1H), 6.60 (s, 4H), 3.60 (s, 2H), 2.40-2.32 (br 8H), 2.21 (s, 3H).

A059: (*E*)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1-methyl-1H-pyrrol-2-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 44% yield. ^{1}H-NMR (DMSO) δ 7.44-7.36 (m, 4H), 7.27 (d, 1H), 7.05 (t, 1H), 6.87 (d, 1H), 6.86 (dd, 1H), 6.60 (s, 4H), 6.14 (dd, 1H), 3.65 (s, 3H), 3.57 (s, 2H), 2.42-3.30 (br, 8H), 2.20 (s, 3H).

A060: (*E*)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-(1H-pyrrol-2-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as orange crystals in 24% yield. ^{1}H-NMR (DMSO) δ 11.58 (1H), 7.44-7.35 (m, 4H), 7.10 (d, 1H), 7.08-7.06 (m, 1H), 6.83 (d, 1H), 6.61-6.60 8m, 1H), 6.59 (s, 4H), 6.19-6.17 (m, 1H), 3.55 (s, 2H), 2.47 (br, 4H), 2.35 (br, 4H), 2.24 (s, 3H).

A061: (*E*)- 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-thiophen-2-yl-propenone

General procedure F gave the oxalate salt of the title compound as slightly yellow crystals in 96% yield. ^{1}H-NMR (DMSO) δ 7.76 (d, 1H), 7.58 (d, 1H), 7.53-7.41 (m, 6H), 7.16 (dd, 1H), 6.93 (d, 1H), 3.65 (s, 2H), 3.05 (br, 4H), 2.66 (s, 3H), 2.55 (br, 4H).

A062: (*E*)- 1,3-Bis-(2-diethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 15% yield. ^{1}H-NMR (DMSO) δ 13.04 (br, 2H), 7.90-7.85 (m, 1H), 7.84 (d, 1H) 7.46-7.28 (m, 7H), 7.03 (d, 1H), 6.62 (s, 4H), 3.69 (s, 2H), 3.47 (s, 2H), 2.43 (q, 4H), 2.29 (q, 4H), 0.87 (t, 6H), 0.76 (t, 6H).

A063: (*E*)- 3-(2,4-Dichloro-phenyl)-1-(3-diethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as orange oil in 15% yield. ^{1}H-NMR($CDCl_3$): δ 8.09 (d, 1H), 7.96 (s, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.61 (d, 1H), 7.50-7.32 (m, 3H), 7.30 (dd, 1H), 3.65 (s, 2H), 2.55 (q, 4H), 1.05 (t, 6H).

A064: (*E*)- 3-(4-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 23% yield. ^{1}H-NMR (DMSO) δ 7.72 (d, 2H), 7.43-7.38 (m, 6H), 7.27 (d, 1H), 7.24 (d, 1H), 6.57 (s, 6H), 3.70 (s, 2H), 3.59 (s, 2H), 2.36 (br, 4H), 2.32 (s, 6H), 2.26 (s, 3H).

A065: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 33% yield. ^{1}H-NMR (DMSO) δ 7.70-7.67 (m, 2H), 7.50-7.40 (m, 6H), 7.25 (d, 1H), 7.21 (d, 1H), 6.56 (s, 4H), 3.67 (s, 2H), 3.57 (s, 2H), 2.34 (br, 4H), 2.32 (br, 4H), 2.30 (s, 6H), 2.20 (s, 3H).

A066: (*E*)- 3-(3-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the fumaric acid salt of the title compound as white crystals in 32% yield. ^{1}H-NMR (DMSO) δ 7.78 (s, 1H), 7.72 (br, 1H), 7.73-7.34 (m, 8H), 6.57 (s, 4H), 3.82 (s, 2H), 3.72 (s, 2H), 2.40 (s, 6H), 2.21 (s, 6H).

A067: (*E*)- 3-(2-Diethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the fumaric acid salt of the title compound as white crystals in 54% yield. ^{1}H-NMR (DMSO) δ 7.91-7, 87 (m, 1H), 7.87 (d, 1H), 7.53- 7.32 (m, 7H), 7.09 (d, 1H), 6.61 (s, 4H), 3.67 (s, 2H), 3.50 (s, 2H), 2.31 (q, 4H), 2.19 (s, 6H), 0.78 (t, 6H).

A068: (*E*)- 3-[3-(Butyl-ethyl-amino)-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the title compound as yellow oil in 3% yield. ^{1}H-NMR (DMSO) δ 7.61-7.29 (m, 4H), 7.23-7.15 (m, 2H), 6.99 (d, 1H), 6.91-6.76 (m, 2H), 6.68 (dd, 1H), 3.53 (s, 2H), 3.37 (q, 2H), 3.37 (q, 2H), 2.14 (s, 6H), 1.60-1.52 (m, 2H), 1.43-1.26 (m, 2H), 1.15 (t, 3H), 0.96 (t, 3H).

A069: (*E*)- 3-(3-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone
General procedure I gave the fumaric acid salt of the title compound as yellow crystals in 45% yield. ^{1}H-NMR (DMSO) δ 8.12 (d, 2H), 7.90 (d, 1H), 7.77 (s, 1H), 7.74-7.72 (m, 1H), 7.64 (d, 1H), 7.37 (d, 2H), 7.04 (d, 2H), 6.51 (s, 4H), 3.82 (s, 3H), 3.55 (s, 2H), 3.01 (t, 2H), 2.62 (t, 2H), 2.57 (s, 6H), 2.13 (s, 3H).

A070: (*E*)-3-(2-Dimethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
General procedure F gave the fumaric acid salt of the title compound as pale brown crystals in 44% yield. ^{1}H-NMR (DMSO) δ 7.90-7.87 (m, 1H), 7.61 (d, 1H), 7.44-7.36 (m, 6H), 7.26-7.24 (m, 1H), 7.00 (d, 1H), 6.57 (s, 3H), 3.58 (s, 2H), 3.28 (s, 2H), 2.40 (br, 4H), 2.32 (br, 4H), 2.20 (s, 3H), 1.95 (s, 6H).

A071: (*E*)- 3-(2-Diethylaminomethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
General procedure F gave the fumaric acid salt of the title compound as white crystals in 44% yield. ^{1}H-NMR (DMSO) δ 7.90 (dd, 1H), 7.77 (d, 1H), 7.43-7.27 (m, 7H), 7.00 (d, 1H), 6.59 (s, 3H), 3.55 (s, 2H), 3.37 (s, 2H), 2.30 (br, 8H), 2.27 (q, 4H), 2.19 (s, 3H), 1.09 (t, 6H).

A072: (*E*)- 1,3-Bis-(2-dimethylaminomethyl-phenyl)-propenone
General procedure F gave the title compound as brown oil in 37% yield. ^{1}H-NMR($CDCl_3$): δ 7.71-7.68 (m, 1H), 7.67 (d, 1H), 7.41-7.20 (m, 7H), 6.93 (d, 1H), 3.57 (s, 2H), 3.29 (s, 2H), 2.11 (s, 6H), 2.03 (s, 6H).

A073: (*E*)- 3-(4-Dimethylaminomethyl-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 39% yield. ^{1}H-NMR (DMSO) δ 7.73 (d, 2H), 7.55-7.42 (m, 4H), 7.39 (d, 2H), 7.32 (s, 2H), 6.59 (s, 4H), 3.65 (s, 4H), 2.29 (s, 6H), 2.14 (s, 6H).

A074: (*E*)- 3-(1H-Indol-5-yl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as yellow crystals in 13% yield. ^{1}H-NMR (DMSO) δ 11.33 (s, 1H), 7.85 (s, 1H), 7.50 (dd, 1H), 7.47-7.35 (m, 7H), 7.09 (d, 1H), 6.47 (t, 1H), 3.54 (s, 2H), 2.26 (br, 4H), 2.15 (br, 4H), 2.00 (s, 3H).

A075: (*E*)- 3-(2,4-Dimethoxy-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 32% yield. ^{1}H-NMR (DMSO) δ 7.75 (d, 1H), 7.63 (d, 1H), 7.57-7.42 (m, 4H), 7.21 (d, 1H), 6.63-6.58 (m, 3H), 6.60 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.69 (s, 2H), 2.22 (s 6H).

A076: (*E*)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-imidazol-1-yl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as pale yellow powder in 17% yield. ^{1}H-NMR (DMSO) δ 8.38 (t, 1H), 7.92 (d, 2H), 7.85 (t, 1H), 7.74 (d, 2H), 7.56-7.43 (m, 4H), 7.38 (s, 2H), 7.13 (t, 1H), 6.61 (s, 2H), 3.65 (s, 2H), 2.14 (s, 6H).

A077: (*E*)-1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

General procedure F gave the oxalate salt of the title compound as yellow crystals in 38% yield. ^{1}H-NMR (DMSO) δ 8.55 (br, 1H), 8.38 (d, 1H), 8.06 (t, 1H), 7.54-7.13 (m, 12H), 3.67 (2H), 2.90 (br, 8H), 2.66 (s, 3H).

A078: (*E*)-3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 14% yield. ^{1}H-NMR (DMSO) δ 8.00 (d, 1H), 7.83 (dd, 1H), 7.44-7.31 (m, 4H), 7.24 (d, 1H), 6.93 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.53 (s, 2H), 2.5 (br, under DMSO, 4H), 2.39 (br, 4H), 2.32 (s, 3H).

A079: (*E*)-3-{3-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-oxo-propenyl}-benzoic acid

General procedure F gave the title compound as brown crystals in 57% yield. ^{1}H-NMR (DMSO) δ 8.15 (s, 1H), 7.93 (t, 2H), 7.49 (t, 1H), 7.52-7.37 (m, 4H), 7.30 (d, 1H), 7.21 (d, 1H), 3.55 (s, 2H), 2.26 (br, 4H), 2.20 (br, 4H), 2.05 (s, 3H).

A080: (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-(2,4-dimethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 50% yield. ^{1}H-NMR (DMSO) δ 7.75 (d, 1H), 7.61-7.56 (m, 2H), 7.50-7.45 (m, 3H), 7.19 (d, 1H), 7.22-7.07 (m, 2H), 6.59 (s, 2H), 3.70 (s, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 2.20 (s, 6H).

A081: (*E*)-3-(2,4-Dimethyl-phenyl)-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as off-white crystals in 32% yield. ^{1}H-NMR (DMSO) δ 7.72 (d, 1H), 7.50 (d, 1H), 7.46-7.39 (m, 4H), 7.11-7.06 (m, 3H), 6.59 (s, 4H), 3.60 (s, 2H), 2.5 (under DMSO, 4H), 2.37 (br, 4H), 2.29 8s, 6H), 2.26 (s, 3H).

A082: (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-(1-methyl-1H-pyrrol-2-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as brown crystals in 22% yield. ^{1}H-NMR (DMSO) δ 7.57-7.40 (m, 4H), 7.39 (d, 1H), 7.07 (t, 1H), 6.99 (d, 1H), 6.92 (dd, 1H), 6.59 (s, 2H), 6.16 (dd, 1H), 3.68 (br, 6H), 2.21 (s, 6H).

A083: (*E*)- 3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as orange crystals in 25% yield. ^{1}H-NMR(DMSO-d_6): δ : 7.68 (s, 1H), 7.46-7.37 (m, 5H), 7.18 (d, 1H), 7.11 (s, 1H), 6.59 (s, 4H), 6.13-6.04 (dd, 1H), 5.04-5.00 (dd, 1H), 4.94-4.88 (dd, 1H), 3.83 (s, 3H), 3.56 (s, 2H), 2.60-2.25 (m, 8H), 2.23 (s, 3H), 1.49 (s, 6H).

A084: (*E*)- 1-(2-Dimethylaminomethyl-phenyl)-3-(4-dipropylamino-2-ethoxy-phenyl)-propenone

(*E*)-3-(4-Dibutylamino-2-fluoro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone (4 mmol), was stirred in 0.1 M sodium ethanolate in EtOH (50 mL) at 25 °C overnight. The solution was evaporated on Celite® and purified by flash chromatography to give the title compound as brown oil in 0.9% yield. ^{1}H-NMR($CDCl_3$): δ : 7.59 (d, 1H), 7.49 (d, 1H), 7.40-7.34 (m, 3H), 7.29 (dd, 1H), 6.96 (d, 1H), 6.23 (dd, 1H), 6.05 (d, 1H), 4.00 (q, 2H), 3.56 (s, 2H), 3.27 (t, 4H), 2.17 (s, 6H), 1.68-1.57 (m, 4H), 1.36 (t, 3H), 0.94 (t, 6H).

A085 : (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as brown crystals in 1% yield. ^{1}H-NMR(DMSO-d_6): δ 7.89-7.86 (m, 1H), 7.70 (d, 1H), 7.46-7.34 (m, 6H), 7.27-7.24 (m, 1H), 7.00 (d, 1H), 6.60 (s, 4H), 3.53 (s, 2H), 3.35 (s, 2H), 2.5 (under DMSO, 4H), 2.20 (br, 4H), 2.20 (s, 3H), 2.08 (s, 6H).

A086: (*E*)- 3-(3-Dimethylaminomethyl-4-methoxy-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 38% yield. ^{1}H-NMR(DMSO-d_6): δ 8.13 (d, 2H), 7.90 (d, 1H), 7.83 (dd, 1H), 7.78 (d, 1H), 7.67 (d, 1H), 7.10 (t, 3H), 6.58 (s, 2H), 3.87 (s, 6H), 3.74 (s, 2H), 2.38 (s, 6H).

A087: (*E*)- 1-(2-Methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 3% yield. ^{1}H-NMR(DMSO-d_6): δ 7.92 (d, 1H), 7.84-7.81 (m, 1H), 7.55-7.49 (m, 1H), 7.43 (dd, 1H), 7.38-7.28 (m, 3H), 7.19 (d, 1H), 7.15 (d, 1H), 7.06 (td, 1H), 6.60 (s, 4H), 3.84 (s, 3H), 3.45 (s, 2H), 2.5 (under DMSO, 4H), 2.30 (br, 4H), 2.24 (s, 3H).

A088: (*E*)-1-(2-Fluoro-4-methoxy-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 15% yield. ^{1}H-NMR(DMSO-d_6): δ 8.12 (d, 1H), 7.87-7.77 (m, 2H), 7.40-7.29 (m, 4H), 7.01-6.91 (m, 2H), 6.60 (s, 3H), 3.87 (s, 3H), 3.56 (s, 2H), 2.5 (under DMSO, 4H), 2.41 (br, 4H), 2.28 (s, 3H).

A089: (*E*)-3-(2-{[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as pale brown crystals in 4% yield. ^{1}H-NMR(DMSO-d_6): δ 7.91-7.88 (m, 1H), 7.75 (d, 1H), 7.50-7.33 (m, 7H), 7.13 (d, 1H), 6.57 (s, 6H), 3.62 (s, 2H), 3.48 (s, 2H), 2.79 (t, 2H), 2.5 (under DMSO, 2H), 2.46 (s, 6H), 2.12 s, 6H), 2.00 (s, 3H).

A090: (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-3-ylamino)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 7% yield. ^{1}H-NMR(DMSO-d_6): δ 8.46 (s, 1H), 8.36 (d, 1H), 8.06 (dd, 1H), 7.64-7.13 (m, 11H), 6.60 (s, 3H), 3.65 (s, 2H), 2.16 (s, 6H).

A091: (*E*)- 3-(2-Dimethylaminomethyl-phenyl)-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as brown oil in 48% yield. ^{1}H NMR ($CDCl_3$) δ8.30 (d, 1H), 7.97-7.94 (m, 2H), 7.79-7.76 (m, 1H), 7.58 (d, 1H), 7.50-7.45 (m, 2H, 7.38-7.35 (m, 3H), 3.55 (s, 2H), 3.53 (s, 2H), 2.29 (s, 6H), 2.26 (s, 6H).

A092: (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-(3-morpholin-4-ylmethyl-phenyl)-propenone

General procedure F gave the title compound as yellow oil in 26% yield. ^{1}H NMR ($CDCl_3$) δ7.98-7.94 (m, 2H), 7.84 (d, 1H), 7.64-7.28 (m, 7H), 3.75 (t, 4H), 3.56 (s, 2H), 3.55 (s,2H), 2.49 (t, 4H), 2.30 (s, 6H).

A093: (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as brown oil in 18% yield. ^{1}H NMR (DMSO) δ 8.31 (d, 1H), 7.94-7.91 (m, 2H), 7.75-7.72 (m, 1H), 7.55 (d, 1H), 7.48-7.39 (m, 2H), 7.33 (dd, 3H), 7.26 (s, 2H), 3.60 (s, 2H), 3.51 (s, 2H), 2.52-2.33 (bs, 4H), 2.26 (s, 6H), 2.25 (s, 3H).

A094: (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-(4-pyridin-2-yl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 3% yield. ^{1}H NMR (DMSO) δ 8.70 (d, 1H), 8.21-7.98 (m, 8H), 7.92 (d, 1H), 7.81 (d, 1H), 7.66 (d, 1H), 7.57 (t, 1H), 3.39 (dd, 1H), 6.60 (s, 2H), 3.74 (s, 2H), 2.32 (s, 6H).

A095: (*E*)-1-(4-Methoxy-phenyl)-3-(3-{[methyl-(2-methylamino-ethyl)-amino]-methyl}-phenyl)-propenone.

General procedure I gave the title compound as slightly yellow crystals in 34% yield. ^{1}H-NMR ($CDCl_3$) δ 8.05 (d, 2H), 7.80 (d, 1H), 7.75 (s, 1H), 7.61-7.57 (m, 1H), 7.56 (d, 1H), 7.48-7.37 (m, 2H), 6.98 (d, 2H), 3.89 (s, 3H), 3.56-3.40 (m, 2H), 3.31 (s, 2H), 2.62-2.56 (m, 2H), 2.20 (s, 9H).

A096: (*E*)-3-(2-Dimethylaminomethyl-phenyl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as slightly yellow crystals in 12% yield. ^{1}H NMR (DMSO) δ 8.10 (d, 1H), 7.98-7.80 (m, 2H), 7.40-7.31 (m, 4H), 7.01-6.92 (m, 2H), 6.59 (s, 3H), 3.87 (s, 3H), 3.50 (s, 2H), 2.14 (s, 6H).

A097: (*E*)-3-(2-Dimethylaminomethyl-phenyl)-1-(2,3,4-trimethoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 17% yield. ^{1}H NMR (DMSO) δ 7.99 (d, 1H), 7.85-7.82 (m, 1H), 7.49-7.28 (m, 5H), 6.94 (d, 1H), 6.59 (s, 4H), 3.87 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.46 (s, 2H), 2.11 (s, 3H).

A098: (*E*)-3-(3-{[(2-Hydroxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as pale yellow crystals in 16% yield. ^{1}H NMR (DMSO) δ 8.17 (d, 2H), 7.93 (d, 1H), 7.84 (s, 1H), 7.78-7.76 (m, 1H), 7.70 (d, 1H), 7.42 (d, 2H), 7.09 (d, 2H), 6.59 (s, 2H), 3.87 (s, 3H), 3.66 (s, 2H), 3.56 (t, 2H), 2.54 (t, 2H), 2.26 (s, 3H).

A099: (*E*)-1-(4-Methoxy-phenyl)-3-(3-methylaminomethyl-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 18% yield. ^{1}H NMR (DMSO) δ 8.15 (d, 2H), 8.04 (s, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.69

(d, 1H), 7.52-7.47 (m, 2H), 7.09 (d, 2H), 6.51 (s, 2H), 4.04 (s, 2H), 3.87 (s, 3H), 2.48 (s, 3H).

A100: (*E*)-1-(3-Dimethylaminomethyl-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone

General procedure F gave the title compound as yellow crystals in 37% yield. ^{1}H-NMR ($CDCl_3$) δ 8.17 (d, 1H), 7.94-7.91 (m, 2H), 7.86 (d, 1H), 7.67 (d, 1H), 7.63-7.57 (m, 4H), 7.55-7.43 (m, 3H), 7.35 (t, 1H), 7.03 (d, 1H), 3.96 (s, 3H), 3.51 (s, 2H), 2.27 (s, 6H).

A101: (*E*)-3-{3-[(2-Methoxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 63% yield. ^{1}H NMR (DMSO) δ 8.15 (d, 2H), 7.97 (s, 1H), 7.94 (d, 1H), 7.80 (d, 1H), 7.70 (d, 1H), 7.49-7.45 (m, 2H), 7.10 (d, 2H), 6.55 (s, 2H), 3.99 (s, 2H), 3.87 (s, 3H), 3.52 (t, 2H), 3.26 (s, 3H), 2.88 (t, 2H).

A102: (*E*)-1-(2-Dimethylaminomethyl-phenyl)-3-[2-methoxy-5-(pyridin-3-ylamino)-phenyl]-propenone

General procedure F gave the title compound as yellow crystals in 35% yield. ^{1}H NMR ($CDCl_3$) δ 8.29 (dd, 1H), 8.13 (dd, 1H), 7.56 (d, 1H), 7.43-7.33 (m, 5H), 7.28-7.22 (m, 1H), 7.18-7.14 (m, 2H), 7.10 (d, 1H), 6.90 (d, 1H), 5.60 (s, 1H), 3.85 (s, 3H), 3.57 (s, 2H), 2.16 (s, 6H).

A103: (E)-3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propanone

Triethylsilane (0.150 mol) was added to a solution of 3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-phenyl)-propenone (0.0075 mol) in trifluoro acetic acid. stirred at 25 °C for 30 hours, before the solution was poured into ice-cold NaOH (2M, 150 mL). Extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated on Celite®. Purified by flash chromatography (EtOAc/heptane, 3% Et_3N). The resulting oil was dissolved in MeOH:Et_2O (1:9 v/v, 10 mL) and a solution of fumaric acid in MeOH:Et_2O (1:9 v/v) was added. The fumaric acid salt of title compound was isolated as white crystals in 24% yield (614 mg).The purity was >95% determined by HPLC. ^{1}H-NMR (DMSO) δ 12.96 (br, 1H), 7.58-7.35 (m, 7H), 6.60 (s, 2H), 3.57 (s, 2H), 3.16 (t, 2H), 3.00 (t, 2H), 2.14 (s, 6H).

A104: *(E)*-3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 61% yield. ^{1}H-NMR(DMSO-d_6) δ 7.83 (t, 1H), 7.62 (d, 2H), 7.63 (d, 1H), 7.47 (dd, 1H), 7.32 (d, 2H), 7.05-6.90 (m, 2H), 6.56 (s, H, fumarat), 3.87 (s, 3H), 2.90-2.68 (m, 4H), 2.39 (s, 6H).

A105: *(E)*-1-(4-Methoxy-phenyl)-3-(3-piperazin-1-ylmethyl-phenyl)-propenone

Prepared by general procedure I using *piperazine-1-carboxylic acid tert-butyl ester* followed by deprotecton using trifluoroacetic acid in methylene chloride. The title compound was isolated as trifluoroacetate salt 43% yield (yellow crystals). ^{1}H-NMR (DMSO-d_6) δ 8.16 (d, 2H), 7.95 (m, 3H), 7.71 (d, 1H), 7.53 (m, 2H), 7.10 (d, 2H), 3.88 (s, 3H), 3.33 (bs, 4H), 3.16 (bs, 4H).

A106: *(E)*-3-(3-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone

Prepared by refuxing A101, formic acid (20 eqv) and formaldehyde (20 eqv) in water for 18 hours. The fumaric acid salt of the title compound was isolated in 70% yield (yellow crystals). ^{1}H-NMR (DMSO d_6) δ 8.16 (d, 2H), 7.89 (d, 1H), 7.79 (m, 2H), 7.69 (d, 1H), 7.42 (m, 2H), 7.09 (d, 2H), 6.61 (s, 2H), 3.87 (s, 3H), 3.63 (s, 2H), 3.49 (t, 2H), 3.24 (s, 3H), 2.61 (s, 3H), 2.24 (s, 3H).

A107: *(E)*-3-(3-{[(2-Amino-ethyl)-methyl-amino]-methyl}-phenyl)-1-(4-methoxy-phenyl)-propenone

General procedure I using *(2-Methylamino-ethyl)-carbamic acid tert-butyl ester* followed by deprotection using Trifluoroacetic acid in CH_2Cl_2. The fumaric acid salt of the title compound was isolated in 10% yield (yellow crystals). ^{1}H-NMR (DMSO-d_6) δ 8.17 (d, 2H), 7.95 (d, 1H), 7.86-7.77 (m, 2H), 7.72 (d, 1H), 7.43-7.41 (m, 2H), 7.09 (d, 2H), 6.41 (s, 2H), 3.87 (s, 3H), 3.57 (s, 2H), 2.94 (t, 2H), 2.59 (t, 2H), 2.14 (s, 3H).

A108: *(E)*-3-{3-[(2-Hydroxy-ethylamino)-methyl]-phenyl}-1-(4-methoxy-phenyl)-propenone

General procedure I gave the fumaric acid salt of the title compound as yellow crystals in 26% yield. ^{1}H-NMR (DMSO-d_6) δ 8.16 (d, 2H), 7.96-7.91 (m, 2H), 7.76 (dt, 1H), 7.69 (d, 1H), 7.46-7.43 (m, 2H), 7.10 (d, 2H), 6.49 (s, 1H), 3.91 (s, 2H), 3.87 (s, 3H), 3.55 (t, 2H), 2.72 (t, 2H).

A109: *(E)*-3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the title compound as yellow crystals in 18% yield.^{1}H-NMR (DMSO-d_6): δ 8,15 (d,2H), 7,86 (t,1H), 7,78 (d,2H), 7,68 (dd,1H), 7,60-7,45 (m,3H), 7,43-7,35 (m,2H), 7,02-6,90 (m,2H), 3,86 (s,3H), 3,50 (s,2H), 2,15 (s,6H).

A110: *(E)*-3-(4-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as orange crystals in 14% yield. ^{1}H-NMR (d_6-DMSO): δ 8.14-8.11 (m, 2H), 7.65 (d, 2H), 7.64 (d, 1H), 7.56 (d, 1H),7.15 (d, 1H), 6.68 (d, 2H), 6.58 (d, 2H), 3.90 (s, 3H), 3.71 (s, 2H), 3.34 (t, 4H), 2.35 (s, 6H), 1.58-1.47 (m, 4H), 1.36 (sixtet, 4H), 0.93 (s, 6H).

A111: *(E)*-3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white powder in 49% yield. ^{1}H-NMR (d_6-DMSO): δ 8.18 (d.2H), 8.04-7.97 (m, 2H), 7.85 (d, 1H), 7.42-7.31 (m, 3H), 7.09 d, 2H), 6.56 (s, 2H), 3.87 (s, 3H), 3.00 (dd, 2H) 2.64 (dd, 2H), 2.39 (s, 6H).

A112: *(E)*-3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as beighe crystals in 34% yield. ^{1}H-NMR (d_6-DMSO): δ 7.67-7.82 (m, 3H), 7.46-7.29 (m, 4H), 7.01-6.92 (m, 2H), 6.56 (s, 2H), 3.87 (s, 3H), 2.97 (dd, 2H), 2.64 (dd, 2H), 2.39 (s, 6H).

A113: *(E)*-3-[2-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as white crystals in 35% yield. ^{1}H-NMR (d_6-DMSO): δ 7.84-7.79 (m, 2H), 7.42-7.38 (m, 2H), 7.37-7.29 (m, 3H), 6.95 (d, 1H), 6.58 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 2.97 (dd, 2H), 2.70 (dd, 2H), 2.42 (s, 6H).

A114: *(E)*-3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as beighe crystals in 43% yield. ^{1}H-NMR (d_6-DMSO): δ 8.18 (d, 2H), 7.93 (d, 1H), 7.83 (d, 2H), 7.70 (d, 1H), 7.36 (d, 2H), 7.10 (d, 2H), 6.57 (s, 2H), 3.88 (s, 3H), 2.92 (bs, 4H), 2.5 (s, 6H).

A115: *(E)*-3-[4-(2-Dimethylamino-ethyl)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 44% yield. ^{1}H-NMR (d_6-DMSO): δ 7.68 (d, 2H), 7.54 (d, 1H), 7.42 (d, 1H), 7.37 (d, 1H) ; 7.33 (d, 2H), 6.94 (d, 1H), 6.55 (s, 2H), 3.88 (s, 3H), 3.84(s, 3H), 3.79 (s, 3H), 2.86 (bs, 4H), 2.47 (s, 6H).

A116: *(E)*-3-(2,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 32% yield. ^{1}H-NMR (d_6-DMSO): δ 8.09 (d, 2H), 8.02 (d, 1H), 7.89 (d, 1H), 7.55 (bs, 1H), 7.40 (d, 2H), 7.04 (bs, 2H), 6.56 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.98 – 2.93 (m, 2H), 2.90 – 2.85 (m, 2H), 2.47 (s, 6H).

A117: *(E)*-1-[4-(2-Dimethylamino-ethyl)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 95% yield. ^{1}H-NMR (d_6-DMSO): δ 8.27 (d, 1H), 8.14 – 8.01 (m, 4H), 7.78 – 7.75 (m, 3H), 7.51 – 7.44 (m, 4H), 7.36 (tt, 1H), 7.22 (d, 1H), 6.57 (s, 2H), 3.95 (s, 3H), 2.96 – 2.90 (m, 2H), 2.85 – 2.79 (m, 2H), 2.43 (s, 6H).

A118: *(E)*-3-(4,2'-Dimethoxy-biphenyl-3-yl)-1-[4-(2-dimethylamino-ethyl)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 27% yield. ^{1}H-NMR (d_6-DMSO): δ 8.12 – 8.06 (m, 3H), 8.02 (d, 1H), 7.91 (d, 1H), 7.56 (dd, 1H), 7.43 (d, 2H), 7.36 (d, 2H), 7.14 (bt, 2H), 7.07 (td, 1H), 6.56 (s, 2H), 3.94 (s, 3H), 3.78 (s, 3H), 2.97 – 2.92 (m, 2H), 2.89 – 2.84 (m, 2H), 2.47 (s, 6H).

A119: *(E)*-3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2,3,4-trimethoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 50% yield. ^{1}H-NMR (d_6-DMSO): δ 8.07 (d, 1H), 8.02 (d, 1H), 7.77 – 7.74 (m, 2H), 7.67 (dd, 1H), 7.51 – 7.36 (m ,6H), 6.95 (d, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.46 (s, 2H), 2.12 (s, 6H).

A120: *(E)*-3-(2,5-Dimethoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 18% yield. ^{1}H-NMR (d_6-DMSO): δ 8.08-8.05 (m, 2H), 7.98 (d, 1H), 7.85 (d, 1H), 7.51 (bs, 1H), 7.03 (d, 2H), 6.96 (d, 1H), 6.59 (s, 3H), 3.94 (bs, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.47 (s, 6H).

A121: *(E)*-3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 4% yield. ^{1}H-NMR (d_6-DMSO): δ 8.01 (dd, 1H), 7.95 (d, 1H), 7.90 (d, 1H), 7.85 (d, 1H), 7.82 (d, 1H), 7.14 (bs, 1H), 6.92 (d, 1H), 6.59 (s, 2H), 6.11 (dd, 1H), 5.03 (dd, 1H), 4.93 (dd, 1H), 3.92 (s, 3H), 3.84 (s, 2H), 2.39 (s, 6H), 2.08 (s, 6H).

A122: *(E)*-3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 41% yield. ^{1}H-NMR (d_6-DMSO): δ 8.22 (d, 1H), 8.08-8.04 (m, 2H), 7.99 (d, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.55 (dd, 1H), 6.92 (d, 1H), 6.60 (s, 2H), 3.85 (s, 2H), 2.40 (s, 6H).

A123: *(E)*-3-(2,4-Dichloro-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 12% yield. ^{1}H-NMR (d_6-DMSO): δ 8.24 (d, 1H), 8.22 (dd, 1H), 8.14 (d, 1H), 8.01 (d, 1H), 7.93 (d, 1H), 7.76 (d, 1H), 7.56 (dd, 1H), 7.18 (d, 1H), 6.58 (s, 2H), 3.92 (s, 3H), 3.64 (s, 2H), 2.3 (s, 6H).

A124: *(E)*-3-[4-Chloro-5-(1,1-dimethyl-allyl)-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 40% yield. ^{1}H-NMR (d_6-DMSO): δ 8.14 (dd, 1H), 8.08 (d, 1H), 7.90 (d, 1H), 7.85 (d, 1H), 7.83 (s, 1H), 7.18 (d, 1H), 7.15 (s, 1H), 6.58 (s, 2H), 6.11 (dd, 1H), 5.04 (dd, 1H), 4.93 (dd, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.69 (bs, 2H), 2.34 (s, 6H), 1.54 (s, 6H).

A125: *(E)*-3-(3',5'-Dichloro-4,6-dimethoxy-biphenyl-3-yl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 45% yield. ^{1}H-NMR (d_6-DMSO): δ 8.18 (dd, 1H), 8.08 (d, 1H), 8.01 (d, 1H), 7.97 (s, 1H), 7.85 (d, 1H), 7.57 (bs, 3H), 7.15 (d, 1H), 6.84 (s, 1H), 6.58 (s, 2H), 4.01 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.65 (s, 2H), 2.31 (s, 6H).

A126: *(E)*-1-(3-Dimethylaminomethyl-4-methoxy-phenyl)-3-(4-methoxy-biphenyl-3-yl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 39% yield. ^{1}H-NMR (d_6-DMSO): δ 8.24-8.20 (m, 2H), 8.09 (d, 1H), 8.06 (d, 1H), 8.00 (d, 1H), 7.77-7.75 (m, 3H), 7.48 (t, 2H), 7.36 (tt, 1H), 7.22 (d, 1H), 7.15 (d, 1H), 6.57 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.58 (s, 2H), 2.27 (s, 6H).

A127: *(E)*-3-(2,4-Dichloro-phenyl)-1-(2-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 34% yield. ^{1}H-NMR (d_6-DMSO): δ 8.10 (d, 1H), 7.73 (d, 1H), 7.68 (d, 1H), 7.62 (d, 1H), 7.51 (dd, 1H), 7.48 (d, 1H), 7.07 (d, 1H), 6.97 (d, 2H), 6.59 (s, 2H), 3.84 (s, 3H), 3.69 (s, 2H), 2.16 (s, 6H).

A128: *(E)*-3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 29% yield. ^{1}H-NMR (d_6-DMSO): δ 8.02-7.98 (m, 1H), 7.95 (d, 1H), 7.76 (d, 1H), 7.62 (d, 1H), 7.21 (t, 1H), 7.09 (d, 1H), 6.97 (bs, 1H), 6.88 (d, 1H), 6.69 (dd, 1H), 6.58 (s, 1H), 3.77 (s, 2H), 3.31 (t, 4H), 2.34 (s, 6H), 1.56-1.46 (m, 4H), 1.32 (sixtet, 4H), 0.93 (t, 6H).

A129: *(E)*-3-(3-Dibutylamino-phenyl)-1-(3-dimethylaminomethyl-4-methoxy-phenyl)-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 66% yield. ^{1}H-NMR (d_6-DMSO): δ 8.16 (dd, 1H), 8.12 (d, 1H), 7.76 (d, 1H), 7.66 (d, 1H), 7.22 (t, 1H), 7.17 (d, 1H), 7.10 (d, 1H), 6.98 (bs, 1H), 6.71 (dd, 1H), 6.59 (s, 2H), 3.91 (s, 3H), 3.69 (s, 2H), 3.31 (t, 4H), 2.34 (s, 6H), 1.56-1.47 (m, 4H), 1.33 (sixtet, 4H), 0.93 (t, 6H).

A130: *(E)*-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-{3-[(pyridin-3-ylmethyl)-amino]-phenyl}-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 28% yield. ^{1}H-NMR (DMSO-d_6): δ 8.60 (d, 1H), 8.44 (dd, 1H), 7.76 (dt, 1H), 7.64 (d, 1H), 7.34 (dd, 1H), 7.24 (s, 2H), 7.14-7.07 (m, 2H), 6.98 (dd, 1H), 6.93-6.91 (m, 2H) 6.68 (dd ,1H), 6.60 (s, 3H), 6.41 (bs, 1H), 4.36 (s, 2H), 3.84 (s, 3H), 3.69 (s, 2H), 2.19 (s, 6H).

A131: *(E)*-1-(2-Dimethylaminomethyl-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow crystals in 86% yield. ^{1}H-NMR (DMSO-d_6): δ 9.06 (s, 1H), 8.21 (d, 2H), 7.53-7.35 (m, 7H), 7.30-7.23 (m, 3H), 6.94 (d, 2H), 6.60 (s, 3H), 3.62 (s, 2H), 2.12 (s, 6H).

A132: *(E)*-1-(2-Dimethylaminomethyl-4-methoxy-phenyl)-3-[3-(pyridin-4-ylamino)-phenyl]-propenone

General procedure F gave the fumaric acid salt of the title compound as yellow-brown crystals in 29% yield. ^{1}H-NMR (DMSO-d_6): δ 8.85 (s, 1H), 8.20 (d, 2H), 7.55 (d, 1H), 7.51 (bs, 1H), 7.44-7.36 (m, 2H), 7.31 (d, 2H), 7.23 (dt, 1H), 7.04 (d, 1H), 6.94-6.91 (m, 3H), 3.82 (s, 3H), 3.56 (s, 2H), 2.07 (s, 6H).

A133: *(E)*-3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-[4-hydroxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

General procedure F gave the title compound as yellow-white crystals in 25% yield. ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H), 7.92 (dd, 1H), 7.78 (d, 1H), 7.48 (d, 1H), 7.47 (d, 1H), 7.41 (d, 1H), 6.89 (d, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.67 (bs, 8H), 2.33 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H).

A134: *(E)*-3-(5-tert-Butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the title compound as orange crystals in 23% yield. ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H), 7.92 (dd, 1H), 7.77 (d, 1H), 7.63 (d, 1H), 7.61 (d, 1H), 7.39 (dd, 1H), 6.89 (dd, 1H), 3.90 (s, 3H), 3.76 (s, 2H), 2.37 (s, 6H), 1.34 (s, 9H).

A135: *(E)*-3-(3,5-Di-tert-butyl-2-methoxy-phenyl)-1-(3-dimethylaminomethyl-4-hydroxy-phenyl)-propenone

General procedure F gave the title compound as orange crystals in 21% yield. ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H), 7.93 (dd, 1H), 7.78 (d, 1H), 7.49 (d, 1H), 7.49 (d, 1H), 7.41 (d, 1H), 6.91 (d, 1H), 3.78 (s, 3H), 3.77 (s, 2H), 2.39 (s, 6H), 1.42 (s, 9H), 1.35 (s, 9H).

A136: *(E)*-3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure E gave the title product as a red oil in 9% yield. ^{1}H-NMR (DMSO-d_6): δ 7.48 (d, 1H), 7.46.7.42 (m, 2H), 7.38 (s, 1H), 7.37-7.24 (m, 2H), 6.96 (d, 1H), 6.48 (s, 1H), 6.21 (dd, 1H), 4.95 (s, 1H), 4.90 (dd, 1H), 3.73 (s, 3H), 3.45 (s, 2H), 2.04 (s, 6H).

A137: *(E)*-3-[5-(1,1-Dimethyl-allyl)-4-hydroxy-2-methoxy-phenyl]-1-(3-dimethylaminomethyl-phenyl)-propenone

General procedure E gave the title product as orange oil in 41% yield. ^{1}H-NMR (DMSO-d_6): δ 7.93 (dt, 1H), 7.93 (d, 1H), 7.88 (br, 1H), 7.56 (d, 1H), 7.54-7.47 (m, 3H), 6.53 (s, 1H), 6.24 (dd, 1H), 4.96 (dd, 1H), 4.91 (dd, 1H), 3.82 (s, 3H), 3.48 (s, 2H), 2.17 (s, 6H), 1.45 (s, 6H).

A138: *(E)*-3-(4-Dimethylaminomethyl-biphenyl-3-yl)-1-(2-dimethylaminomethyl-phenyl)-propenone

General procedure F gave the title compound as beighe crystals in 57% yield. ^{1}H-NMR (DMSO): δ 8.12 (d, 1H), 7.80-7.77 (m, 2H), 7.69 (d, 1H), 7.63 (d, 1H), 7.50-7.36 (m, 7H), 7.34 (d, 1H), 7.23 (d, 1H), 3.52 (s, 2H), 3.31 (s, 2H), 2.02 (s, 6H), 1.98 (s, 6H).

A139: *(E)*-1-(2-Dimethylaminomethyl-phenyl)-3-{3-[(pyridin-3-ylmethyl)-amino]-phenyl}-propenone

General procedure F gave the title compound as yellow oil in 30% yield. ^{1}H-NMR (DMSO-d_6): δ 8.58 (d, 1H), 8.43 (dd, 1H), 7.75 (dt, 1H), 7.47-7.31 (m, 5H), 7.12-7.00 (m, 3H), 6.87-6.85 (m, 2H), 6.68 (bd, 1H), 6.39 (t, 1H), 4.35 (d, 2H), 3.46 (s, 2H), 2.00 (s, 6H).

Determination of metabolic stability

Incubations were performed with Wistar rat liver microsomes (0.25 mg/ml) in 2% sodium bicarbonate solution. NADP (0.13 mg/ml), glucose-6-phosphate (0.63 mg/ml) and glucose-6-phosophate dehydrogenase (0.38 units/ml) were used as NADPH generation system and UDPGA (0.48 mg/ml) was added to include the phase II reaction, glucuronic acid conjugation, in the assay. After 5 minutes of pre-incubation the reaction was started by addition of the test article to give a final concentration of 20µM. Samples were incubated for 15 min at 37°C and the reactions were terminated by addition of equal volumes of acetonitrile. Blank incubations were performed at the same concentration but without addition of microsomes. Both blank and microsome-containing samples were made in replicats of three. Prior to analysis samples were centrifuged for 10 min. at 3500 rpm,HPLC system:

The fraction of compound metabolised during the 15 min of incubation was determined by comparison of blank and microsome-containing samples using a Waters Alliance 2690 separation module and Waters 996 PDA-detector(Waters. Milford, MA, USA.) Separation was performed on a XTerra MS C_{18} column (150*2.1 mm I.D., 3,5 µm particle size) (Waters Milford, MA, USA) by. Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile phase B (10 mM ammonium acetate pH 9.5). During the first 20 minutes, the mobile phase was changed via a linear gradient to 90% A and 10% B. This was followed by a 5 minutes linear gradient to initial conditions, which were maintained for 5 min. The flow rate was 0.20 ml/min and injection volume 10 µl.

Determination of solubility

Solubility of the compounds was determined by preparing a saturated solution of compound in 0.3 M phosphate buffer (pH 7.4 ± 0.3) in a brown glass tube. The suspensions were rotated slowly for 24 hours. Aliquots were centrifuged for 10 minutes at 14.000 rpm and supernatants were diluted in 40% (v/v) acetonitrile in water prior to HPLC analysis. Concentrations of analytes were quantified against a standard curve and used as term of solubility.
The HPLC-UV method used for the assessment of solubility is the same as used in the *in vitro* metabolism assay.

Pharmacokinetic Studies

Evaluation of the pharmacokinetic properties of the compounds was done using female NMRI mice (weighing app. 30 g). Test articles were administrated intravenously and orally as a cassette dose formulations containing three compounds or as individual compounds. Samples of serum were taken at defined timepoints.

Standards and QC-samples in plasma were prepared and the serum concentrations of the test compounds quantified by HPLC-MS.
Prior to analysis, proteins were precipitated by deluding the samples (1:1) (v/v) with 100 % acetonitrile followed by centrifugation at 14.000 rpm in 10 min. The supernatant was used for the analysis.

HPLC-MS system:

A Waters Alliance HPLC-system (Milford, MA, USA) was coupled to a Quatro Micro triple quadropl mass spectrometer (Micromass, Manchester, UK) operating in positive (ESI) mode. Separation was performed on a XTerra MS C_{18} column (150*2.1 mm I.D., 3,5 µm particle size) (Waters Milford, MA, USA).
Mobile phase A: 0.1% (v/v) formic acid or 10 mM ammonium acetate pH-adjusted to 9.5 in MilliQ-water, mobile phase B: 100% methanol. The gradient was as follows: 0 min = 70%A – 30% B, 0-10 min. a linear gradient to 10% A and 90 % B this was maintained till 11 min, 11-13 linear gradient to 70% A and 30% B this was maintained till 18 min. The flow rate was 0.20 ml/min, injection volume 10 µl.

Biological testing

General methods

***In vitro* microbiological testing**

MIC determination in broth microdilution assay

Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus ATCC29213; Staphylococcus aureus ATCC33591;Staphylococcus intermedius #2357(clinical isolate from the Copenhagen*

area); Enterococcus faecalis ATCC29212;Enterococcus faecium #17501 (vancomycin-resistant clinical isolate); Streptococcus pneumoniae #998 (clinical isolate); Streptococcus pyogenes #14813 (clinical isolate); Streptococcus agalactiae #19855 (clinical isolate); Eschericia coli ATCC25922 and Eschericia coli ESS). The screening assay was done in 200 µl MH-broth cultures in microtitre plates. For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by *NCLLS* (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition. M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate. MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria. MICs for ATCC type strains fell within the limits posted by the *NCCLS* (National Committee for Clinical Laboratory Standards. Performance Stadards for Antimicrobial Susceptibility Testing; Eleventh Informational Supplement. M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin.

MIC and MBC determination in broth macrodilution assay

MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5x10E5 CFU/ml as described by Amsterdam (Amsterdam, D. Susceptibility testing of antimicrobials in liquid media. *In* V.Lorian (ed.): Antibiotics in Laboratory Medicin 4. edition. Williams & Wilkins 1996). MIC was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria. Samples from cultures inhibited by test compound were plated onto unselective blood agar plates. MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0.1% compared to the original inoculum.

Killing Curve determination

For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5x10E5 CFU/ml as described for the MIC macrodilution assay above. At the timepoints indicated 100 µl samples was withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar plates to determine CFU. Test compounds with bactericidal activity is capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria. Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound. An example of a bactericidal compound (A031), which is primarily dependent on the concentration of the test compound is shown in Figure 3. An example of a bactericidal compound (A019) which is primarily dependent on the incubation time with the compound is shown in Figure 4.

MIC determination against Helicobacter pylori

Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the standards of NCCLS (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition. M7-A5 NCCLS 2000). MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 µl spots of a 2 McF suspension of the different strains of *H.pylori*. This inoculum corresponds to approximately 10E6 CFU/spot. Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours. The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds.

Activity determination against anaerobic bacteria

Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis,* an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Fifth Edition. M11-A5 NCCLS 2000) with the exception that Mueller-Hinton agar was used in place of supplemented Brucella broth. Plates containing test compound at a single concentration (either 100 or 150 µM) were prepared in duplicate along with appropriate control plates. Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not containg test compound.

Leishmania promastigote assay

A WHO reference vaccine strain of *L.major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks' Salts containing 0.02 mg/ml gentamycin, 25 mM HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS). Incubation was carried out at 27°C. Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth.
The effect of test compounds on promastigotes was assessed by a method modified from Pearson et al. Briefly, promastigotes ($0.8x10^6$/well) were incubated in 200 µl duplicate cultures either with a dilution series of test compound or medium alone in 96 wells flat buttom microtiter plates. After 2h of incubation, 1.5 µCi of 3H-thymidine was added to each well and further incubated for 18 hours. The cultures were then harvested on Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

Plasmodium falciparum assay

Plasmodium falciparum 3D7 was maintained in culture by a modification of the method originally described by Trager and Jensen. In brief, the parasites were grown in suspensions of human blood group 0 erythrocytes (RBC) maintained in RPMI1640 medium

supplemented with 4.5 g/l Albumax II (Invitrogen), 10 mM hypoxantine, 1.4 mM L-glutamine and 0.05 mg/ml gentamicin. Cultures were incubated at 37°C in atmosphere of 92.5% nitrogen, 5.5% carbon dioxide, and 2% oxygen. To obtain synchronized cultures og parasites erythrocytes infected with late trophozoite and schizont stages were separated from ring stages and uninfected RBC by magnet-activated cell sorting (MACS; Miltenyi BioTec) (Staalsoe, T., H.A. Giha, D. Dodoo, T.G. Theander, and L. Hviid. 1999. Detection of antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow cytometry. Cytometry 35:329-336). Because of their high content of paramagnetic haemozoin, erythrocytes infected with late developmental stages of malaria parasites are specifically retained within the column. The column was washed with PBS supplemented with 2% foetal calf serum and then the column was removed from the magnet and the retained late developmental stages of parasites were eluted and cultured for an additional 18 hours. At this time the culture is highly synchronous containing more than 90% ring stages.

These synchronized cultures of ring stage parasites were used to assay for antimalarial parasites. Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by addition of uninfected RBC. Then, these were incubated in 125 µl duplicate cultures containing $2.5x10^7$ RBC/well with either a dilution series of test compound or with medium alone. Plates were then incubated at 37°C for 24 hours when cultures were labelled by the addition 1.1 µCi 3H-phenyalanine and incubated overnight. Then, the cultures were harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed extensively with water followed by a wash with 10% H_2O_2 to bleach hemoglobin. Filter plates were counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

DHODH Assay

100 µl chalcone or 0.1 M Tris-HCl pH 8.0 is added to a well in a 96-wells microtiter plate. Then 50 µl enzyme dilution is added. The microtiter plate is placed in the Powerwave$_x$340 and the enzymatic reactions starts when adding 100 µl assay mixture. The reaction are measured every 20 sec. for 10 min. The samples with chalcones are compared with the samples with 0.1 M Tris-HCl pH 8.0 and the percent inhibition is calculated.

Enzyme dilution: The solution of recombinant purified enzyme is dissolved in 0.1 M Tris-HCl pH 8 to give an initial velocity of 0.04 - 0.05 ΔA/min.

2,6-dichlorophenolindophenol (DCIP)-stock solution: 40 mg DCIP and 10 ml 99 % Ethanol are mixed for 10 min at RT. Then 100 µl 1.0 M Tris-HCl pH 8 and miliQ H_2O are added to a final volume of 100 ml. The A_{600} of the DCIP-stock solution are measured in a microtiter plate on the Powerwave$_x$340 (Bio-Tek instruments,Inc.)

Dihydroorotate dehydrogenase (DHODH)-stock solution: 25 mM dihydroorotate stock-solution is prepared by first dissolving in the same amount of mol NaOH and then miliQ H_2O is added to the final volume.

Assay mix (10 ml solution): 600 µl of DHODH-stock solution and X ml (depending on the A_{600} value of stock-solution) DCIP to a final A_{600} = 2.5 are mixed. Then 0.1 M Tris-HCl pH 8.0 are added to a final volume of 10 ml.

Preparation of compound soluton: A 10 mM stock-solution of compound (e.g. a chalcone derivative) is made in dimethylsulfoxid (DMSO). The compound is then diluted in 0.1 M Tris-HCl pH 8 to the test concentrations. The final DMSO concentration in the sample is 10%

In vivo models

Effect of Chalcones Following Multiple Intra venous Administration in Plasmodium berghei K173 Infected NMRI Female Mice.

Animals in groups of 6 were inoculated intra peritoneally with $1x10^6$ infected red blood cells (RBC). On day 4 after infection, when the parsitaemia was 2-5%, treatment was initiated and the animals were dosed, according to the body weight recorded, once daily for 3 consecutive days (day 4-7). The doses stated were administered intra venously as solutions in a suitable vehicle. Parasitaemia, as percentage infected blood cells, was determined by counting 500 RBCs in stained (Giemsa) blood smears, prepared from blood samples from the tail vein taken on day 4 to 9 after infection.

Effect of Chalcones Following Multiple Oral Administrations in Plasmodium berghei K173 Infected NMRI Female Mice.

Animals in groups of 4 were inoculated intra peritoneally with $1x10^6$ infected red blood cells (RBC). 2 hours after infection, treatment was initiated and the animals were dosed, according to the body weight recorded, twice daily for 3 consecutive days (day 0-3). The doses stated were administered orally as solutions in a suitable vehicle. Parasitaemia, as percentage infected blood cells, was determined by counting 500 RBCs in stained (Giemsa) blood smears, prepared from blood samples from the tail vein taken on day 6 after infection.

Biological Results

Licochalcone A (LicA) and 4'methoxy chalcone (4'MC) described in WO 93/17671 are used as reference compounds in the following discussion.

Activity against non-fastidious bacteria:

Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-positive non-fastidious bacteria including *Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Streptococcus agalactiae*. Licochalcone A maintains its activity also against antibiotic resistant bacteria, e.g. *Staphylococcus aureus ATCC33591* (resistant to methicillin) and *Enterococcus faecium #17051* (resistant to vancomycin). In contrast, Licochalcone A have only modest or no activity against the prototype pathogenic Gram-negative bacterium,

Eschericia coli. 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial effect at all.

In comparison with Licochalcone A, aminochalcones retain the activity of Licochalcone A against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf. Table 1). Several aminochalcones exhibit increased potency against Gram-positive pathogens (e.g. A025, A030, A019, A033, A083). In contrast to Licochalcone A, aminochalcones exhibit activity against *Eschericia coli*. Thus, several aminochalcones (e.g. A030, A031, A019, A083, A084) exhibit considerable activity against the ESS strain of *E.coli*, which generally is more susceptible to antibiotics than the type strain *E.coli ATCC25922*. However, several aminochalcones (e.g. A022) exhibit similar high activity against both Gram-positive bacteria and *E.coli ESS* and *ATTC 25922* strains. Thus, aminochalcones can be modified to permeate and inhibit Gram-negative bacteria. This indicates the potential use of aminochalcones in the treatment of infections with Gram-negative bacteria.

In the treatment of severe infections in immunocompromised patients bactericidal action of a antibiotic is a necessity. As exemplified in Figures 3 and 4, aminochalcones retain the bactericidal action of Licochalcone A. For some aminochalcones the bactericidal action is predominantly dependent on the concentration of the compound (e.g. A031; cf. Figure 3); for others the bactericidal action is predominantly dependent on the time of incubation with the compound (e.g. A019; cf. Figure 4). This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials.

Tabel 1. Comparasion of the effect of amino-chalcones and Licochalcone/4'MC on bacteria; MIC values in µM.

	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*
LICA	37.5	37.5	37.5	37.5	37.5	75.0		300.0
4'-MC	NA	NA	NA	NA	NA	NA	NA	NA
A025	9.4	9.4	9.4	9.4	9.4	37.5		75.0
A030	9.4	9.4	9.4	18.8	18.8	18.8		18.8
A019	9.4	9.4	9.4	9.4	9.4	18.8		18.8
A033	4.7	9.4	4.7	9.4	9.4	75.0		150.0
A083	9.4	9.4	18.8	18.8	9.4	18.8		9.4
A022	37.5	37.5	37.5	18.8	18.8	18.8	18.8	18.8
A117	9.4	9.4	9.4	37.5	37.5	37.5	150	9.4
A137	4.7	9.4	9.4	9.4	9.4	37.5		
A129	4.7	9.4	9.4	9.4	9.4	37.5		9.4

***A**:Staphylococcus aureus ATCC29213; **B**:Staphylococcus aureus ATCC33591 (resistant to methicillin); **C**: Staphylococcus intermedius #2357(clinical isolate from the Copenhagen*

*area); **D**: Enterococcus faecalis ATCC29212; **E**: Enterococcus faecium #17501 (vancomycin-resistant clinical isolate); **F**: Streptococcus pneumoniae #998 (clinical isolate); **G**: Eschericia coli ATCC25922 and **H**: Eschericia coli ESS.* NA: no activity.

Activity against Helicobacter pylori:

Colonization of the gastric mucosa with *Helicobacter pylori* is an important pathogenic determinant for the development of gastritis and peptic ulcer. Aminochalcones exhibit activity against *Helicobacter pylori.* Several aminochalcones (e.g. A026, A035, A037, A038, A045, A051, A063, A118, A124) exhibit MICs in the range between 12.5 μM and 100 μM when tested against a panel of six strains *Helicobacter pylori*, that includes strains resistant to metronidazole. Metronidazol is an antibiotic commonly included in treatment regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer. The activity of aminochalcones against both metronidazole-resistant and sensitive *Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment of *Helicobacter* infections.

Activity against anaerobic bacteria:

Aminochalcones have been assayed in a single concentration of compound (100 μM) for activity against a panel of anaerobic bacteria containing common human pathogenic bacteria (*Bacteroides fragilis, Clostridium perfringens, Clostridium difficele*). Several aminochalcones (e.g. A011, A026, A034, A037, A038, A063, A090) exhibit activity against all microorganisms within the test panel. This clearly indicates the potential use of aminochalcones in treatment of infection caused by anaerobic bacteria.

Activity against protozoa:

Activity against Plasmodium falciparum:

Plasmodium falciparum is a protozoan parasite transmitted by the mosquito, *Anopheles*, and causing malignant or severe malaria in humans. Licochalcone A exhibit activity against *Plasmodium falciparum in vitro* and protects mice from infection with *P.yoelii* and *P.berghei* (Chen et al., 1994). Aminochalcones exhibit activity *in vitro* against *Plasmodium falciparum* and several aminochalcones exhibit improved potency compared to Licochalcone A (cf. Table 2 and Figure 5). Futhermore the compounds are potent against chloroquine resistant parasites as shown in Table 3. The results clearly indicate the potential use of aminochalcones in the treatment of malaria.

Table 2 Activity against Plasmodium falciparum 3D7.

Comp.	*LicA*	*4'MC*	*A027*	*A035*	*A038*	*A043*	*A066*	*A090*	*A102*
IC_{50} (μM)	6.4	40.0	0.7	0.9	1.2	1.3	0.9	1.0	0.5

Comp.	*A127*	*A130*	*A131*	*A132*	*A139*	*A141*
IC_{50} (μM)	0.6	0.5	0.5	0.6	0.4	0.7

Table 3. Activity against resistant strains of Plasmodium falciparum

	Plasmodium falciparum IC_{50} (μM)			
	3D7(Cq-sen)	DD2 (Cq-res)	7G8(Cq-res)	K1(Cq-res)
A027	0.7	1.1	1.1	1.1
A102	0.5	1.2	1.1	1.1
Chloroquine	0.13	1.0	1.09	>1.56

Activity against Leishamania major:

Leishamania major is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and causing cutaneous leishmaniasis or kala-azar in humans. Licochalcone A exhibit activity against *Leishmania* parasites and has shown efficacy in experimental animal models of cutaneous and visceral *Leishmania* infection (Chen et al., 1994). Aminochalcones exhibit activity *in vitro* against *Leishamania major* with significantly improved potency compared to Licochalcone A and 4'MC (cf. Table 4 and Figure 6). The results clearly indicate the potential use of aminochalcones in the treatment of *Leishamania* infection.

Table 4. Effect of amino-chalcones on *L. major*.

Comp.	*LicA*	*4'MC*	*A027*	*A034*	*A035*	*A037*	*A038*	*A051*	*A063*	*A083*	*A100*
IC_{50} (μM)	4.6	5.6	0.2	0.9	0.3	0.1	0.8	0.5	0.9	1.0	0.2

Inhibition of DHODH.

Several of the amino-chalcones prepared are potent inhibitors of DHODH. The compounds are as potent as LicA and by far more potent than ordinary chalcones exemplified by 4'MC.

Table 5. Inhibition of DHODH.

Comp.	*LicA*	*4'MC*	*A020*	*A021*	*A022*	*A025*	*A035*	*A038*	*A045*
Inhibition	25%	7%	23%	27%	28%	26%	26%	22%	20%

Metabolism

The usefulness of chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* (Lica: 100% turn-over *in vitro* and $t_{1/2}$= 10min *in vivo*).

The introduction of an amino group in the chalcone changes the metabolic properties; this is clear from Table 6 where the metabolic turn-over of a number of amino-chalcones are compared to LicA. The amino-chalcones prepared are expected to show low or no metabolism *in vivo* as the metabolic turn-over are between 0-10% (compared to 100% turn-over for Lica). Consequently, the half-life of an amino-chalcone will be longer, reducing the dose needed for treatment.

Table 6. Metabolic turn-over (rat) in vitro (%).

Comp.	*LicA*	*A010*	*A019*	*A029*	*A049*	*A099*	*A102*	*A110*
Turn-over	100%	1%	5%	3%	0%	7%	2%	6%

Solubility

The aqueous solubility of the neutral chalcones described in WO 93/17671 is very low. A representative chalcone 4'-methoxy-chalcone has a solubility of <<0.05 mg/ml. A few chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the molecule. LicA has a solubility of approximately 0.01 mg/ml.

The amino-chalcones described in this application are by far superior having solubility numbers in mg/ml (cf. Table 7).

Table 7. Solubility in aqueous buffer at pH 7.4.

Comp.	*A005*	*A010*	*A013*	*A049*	*A066*	*A069*	*A086*
Solubility (mg/ml)	>6	33.4	31.2	6.3	7.4	>10	8.9

The high solubility means that dissolution and hence absorption will be no problem. This will inevitably cause a dramatic reducing of the dose needed making the amino-chalcones very usable as drug candidates.

Bioavailabiblity

The bioavailability of the amino chalcones in mice is in general very high (e.g. 34% for A048). As the mouse is a very fast metabolizer of the amino chalcones compared to rat and human (e.g. A102 mice: 28%; rat: 2%; human: in general lower than rat) the bioavailability in rat and man is expected to be even higher due to limited first pass metabolism.

In vivo results

A number of amino-chalcones have significant effect in the *in vivo* models. As illiustrated on figure 7 and 8 the compounds cause a significant reduction of parasitaemia in plasmodium infedted mice, showing the potential of the compounds as drug candidates.

Conclusion: The use of chalcones as drug candidates for the treatment of parasitic or bacterial infections have been limited by the low in vivo potency of the compounds and a narrow spectrum of activity.

Several factors contribute to the low in vivo potency: Fast metabolism resulting in short half-lives in vivo; Low/no solubility in the intestine and consequently low/no absorption; Medium potency of the compounds against parasites and no activity against bacteria (except for LicA).

The amino-chalcones in this application are expected to fulfill the criteria for a drug candidate. The metabolism is low, the solubility is high and the compounds are potent against parasites as well as (resistant) Gram positive and Gram negative bacteria.